CAPILLARY BLOOD SAMPLING: ARE THE RESULTS COMPARABLE TO VENOUS SAMPLING IN HEALTH AND DISEASE

By

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Abstract

Background: Blood gas analyser (BGA) results are used to guide treatment, however their accuracy for some parameters is unknown. Blood tests taken from capillary blood can also be analysed by a BGA but again the accuracy is unknown.. Capillary and venous BGA tests were compared to gold standard tests for sodium, potassium, haemoglobin, glucose and lactate.

Methods: 23 healthy adults and 48 acutely unwell diabetic patients had ear lobe prick (EP) and finger prick (FP) (capillary) and standard venous blood samples. Venous samples went for standard laboratory (VL) reporting as well as being analysed in the BGA (VBG). Results were compared to international acceptability criteria. All studies had ethical approval (NRES14/WM/1057).

Results: VBG and EP sodium results met the acceptability criteria. FP samples marginally failed with 94.8% meeting the required level (95% within 4mmol/l of VL result). All potassium, haemoglobin and lactate samples failed to reach the required level of accuracy (95% within 0.5mmol/l, 5g/l and 0.5mmol/l respectively). Potassium FP and EP samples were more accurate than the VBG results ($p<0.001$). VBG glucose in the hyperglycaemic range met acceptability criteria (within 20% of VL) as did FP when values were >12mmol/l.

Conclusions: BGA results are sufficiently accurate for the analysis of sodium. FP and VBG glucose are suitable in hyperglycaemic ranges only. Capillary samples could be used as an alternative to VBG potassium if considering BGA measurement only. Results for other parameters should be used as a guide rather than as a definitive value.

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1. Introduction

1.1 Background and Rationale

Close monitoring of physiological parameters is known to improve patient outcome in many disease states. Rapid correction of electrolyte abnormalities in conditions such as diabetic ketoacidosis has been shown to reduce morbidity as well as the length of stay in hospital.(Matoo VK 1991, Wagner A 1999, MacIsaac RJ 2002, Jayashree M 2004, Solá E 2006, Armor B 2011) Close monitoring of sodium is critical to prevent irreversible neurological sequalae such as cerebellar pontine myelinolysis and extra-pontine myelinolysis.(Karp BI 1993, Laureno R 1997, Chakraborty S 2013) For these reasons the necessity of close biochemical monitoring has been emphasised by various national bodies such as the Joint British Diabetes Society (JBDS), Renal Association UK and the National Institute for Clinical Excellence.(Alfonzo A 2014, Group 2014, Hospital 2014).

In conditions such as hyperglycaemia, hyperkalaemia, hyponatraemia and diabetic ketoacidosis, it is common to perform serial venepunctures during a single day to guide electrolyte replacement therapy as recommended by current guidelines, including from the JBDS on pathways for the management of DKA.(Group 2014) There can be practical difficulties complying with these recommendations. Venepuncture is one of the most painful procedures and one of the most frequently performed ones (Taddio A 2002, Deacon B 2006) and anxiety associated with venepuncture is a common problem. This anxiety can prevent a patient agreeing to repeat blood tests, affecting a patient's ability to receive medically essential treatment (Deacon B 2006). Patients with acute illness can have poor venous access, and oedema and obesity can hinder serial testing. Delirium associated with illness can also

hamper compliance with treatment. Once a sample is taken, rapid correction of electrolytes abnormalities is limited by the speed at which clinical laboratories can process and report biochemical analyses of venous samples, a process which can take several hours.

These factors have driven the proliferation of analysing blood using point-of-care testing (POCT)(Howanitz JH 2001), where blood samples are taken to an analyser at or near the patient's bedside or immediate environment and processed to get an result within a few minutes. Improved patient outcomes and reduction in the length of hospital stay are seen as one of the main advantages of point of care testing(Grieve R 1999). Using blood gas analysers as a POCT method may provide a rapid assessment of gross electrolytes and haematological disturbances. However, since venepuncture is the most common method of blood sampling for this method of POCT, it continues to cause anxiety, pain and subsequent hyperalgesia (Taddio A 2002, Deacon B 2006). The current modality of blood sugar monitoring in diabetic patients and triaging hospital admissions involves bedside capillary blood glucose meters. Their use has been validated in clinical environments and is recommended in the Joint Diabetes Society Guidelines for continuing monitoring of blood glucose (Arabadjief D 2006, Thomas LE 2008, Boren SA 2010). While the validity of capillary blood glucose measurement by glucose meters is known, the validity of glucose measurement in capillary heparinised samples run through a blood gas analyser is unknown in adult patients. Blood gas analysers can also provide Na, K, Hb, Lactate, PaO2, $PaCO_2$, Glucose and HCO3 but only capillary O_2 (kPa), CO_2 (kPa), glucose and ketones (using specialist meters) have been validated in adults, although there has been study in paediatric populations.

Capillary blood sampling offers several advantages in the acute setting. Firstly the relative ease of obtaining the samples compared to venepuncture. There are several collection sites on the body and these can be rotated (heel, fingertip, earlobe) and testing can be performed with minimal training by medical, nursing and ancillary healthcare staff. Blood gas analyses provide an almost immediate result, which may speed clinical decisions regarding care. Capillary sampling is believed to be less painful, and this may facilitate serial testing in the frail, anxious or those without capacity. Also, serial testing will not impact on venous access points which can then be used for intravenous medications and fluids and avoid cannulation in sites more prone to infection such as the lower limbs or the requirement of invasive central venous access. Patients in hospital, particularly diabetic patients, are also frequently having capillary blood taken for glucose monitoring when on intravenous insulin (often required hourly in this case) or during their standard blood glucose monitoring regimens. If this blood could be taken for measurement of other the parameters listed above at the same time this could reduce the overall number of blood tests taken but also allow very close monitoring of these crucial biochemical and haematological tests. If capillary blood gas analyses were accurate enough to inform clinical decisions, these advantages would be of significant value to patient care.

There are, however, several potential disadvantages to capillary blood sampling. It is unclear if other values derived from POCT testing (for example: Na, K, Hb, lactate, glucose using a blood gas analyser) are accurate enough to guide clinical care. Only a limited amount of blood can be obtained by this sampling modality and therefore analysis needs to be focused on a small number of parameters. The standard capillary tube, which can be used in blood gas analysers can take approximately 120 microlitres and needs to be full to process all the

required results. Acquiring this volume of blood may be difficult if flow is poor or there is inadequate puncture. Scarring can occur when there have been multiple puncture sites in the same area and it has been hypothesised that damage to blood cells may cause inaccurate test results such as an artificially high potassium or low haemoglobin, but this has not been proven.

1.2 Current Methods of Point of Care Blood Testing in Emergency Care and the Evidence for them

For the reasons discussed POCT is being used for many different biochemical and haematological parameters. However, the blood analysed is often different to the standard analysis methods for example point of care analysers uses whole blood, often this will have heparin incorporated into the collection device, whereas laboratory samples use several different types of blood and reagents. These include serum samples used for most electrolytes and biochemical tests that contain gel separators which will enable the serum to be easily removed following centrifugation. There are also plasma samples, used for glucose and lactate measurements, which are derived from centrifuged whole blood containing an antiglycolytic agent and an anticoagulant. EDTA samples are used for full blood count assessment; this is a potent anticoagulant and enables blood cell measurement. So differences in processing and also subsequent analysis occurs within different time frames with POCT being processed within minutes but laboratory samples taking up to several hours to be processed. They are transported differently as well, with POCT samples being transported usually very short distances by hand, whereas laboratory samples may be transported by pneumatic pods, hospital transport or portering services. Most of the POCT analysers have direct ion-selective electrodes, which measure the activity of ions in plasma. In contrast, the central laboratory analyser has indirect ion-selective electrodes and measures the

activity of ions in pre-diluted sample and is affected by dissolved solids such as proteins, hence influencing the values obtained by various electrodes. (Dheeraj Kapoor1 2014) These differences may cause clinically significant differences in the parameters being analysed. For these reason many authors have attempted to compare point of care testing to standard testing results. These papers will now be discussed including the different parameters currently being measured by POCT, the evidence behind them and their reliability in guiding clinical care.

1.2.1 Blood gas analysis

Arterial blood gas analysis is a well-established method of assessing patients who are acutely unwell to assess patients' blood oxygen levels (pO_2), carbon dioxide level (pCO_2), and acid base balance. This is a very painful procedure and can be associated with serious complications including arterial vessel intimal tears and ischaemia to the hand.(Mortensen 1967, Roberts J 1998) For this reason studies have looked into using alternatives such as venous sampling to see if these would produce similar results.

In a number of studies venous and arterial blood have been shown to produce concordant values for pH and bicarbonate (HCO_3) (Gokel Y 2000, Kelly A M 2001, Ma O J 2003, Kelly A M 2004). To study the differences between samples some authors report the mean difference, which is the same as mean bias, and also the R^2 or the coefficient of determination. This is a statistical test that summarises how close the data fits a statistical model with values closer to 1 representing the closest fit.

The first of these studies by Kelly 2001 who looked at venous pH compared to arterial pH in 246 patients presenting to the emergency department, who the attending doctor deemed requiring an ABG. This included 195 adult patients with acute respiratory disease and 51 with suspected metabolic derangement. It showed good levels of agreement when compared to arterial pH with a mean difference of -0.04 and 95% limits of agreement (LOA) from -0.11 to +0.04. The same author added further analysis to these results in 2004 by comparing agreement of bicarbonate and showed a mean difference of 1.2 mmol/L with 95% LOA from -2.73 to +5.13 (Kelly A M 2001, Kelly A M 2004). Other studies have focused on adult patients presenting to the emergency department with DKA with Ma in 2003 and Gokel in 2000 comparing the results of paired ABG and VBG for pH and bicarbonate. This was assessed in 195 and 152 patients respectively and again showed no significant difference between the two. Gokel also included 33 healthy controls in this study and showed differences in the means between arterial and venous pH in this healthy group to be 0.05 +/- 0.01 (standard error) and for bicarbonate -1.66 +/- 0.58 mmol/l, with a correlation in this group (R^2) of 0.60 and 0.55 respectively. This was a weaker correlation than found in the DKA group where R^2 was 0.99 and 0.99, respectively. The healthy control group were younger than those patients within the DKA group (age ranges of 18-65) but the authors offered no further details about this group nor potential reasons for this difference.

A meta-analysis including 18 studies agreed that there was little clinically significant difference in pH and showed arterial pH to typically be 0.030 higher than the venous pH (95% confidence interval 0.029 to 0.038). This analysis also concluded that the pCO2 values with variations between venous and arterial of -1.43 kPa to +0.33kPa (within the 95% confidence

interval) were unacceptably wide for clinical use (Byrne AL1 2014). Another meta-analysis had similar conclusions but considered a normal venous pCO_2 a good negative predictor of significant hypercapania compared to an arterial sample allowing a venous test to rule out significant hypercapnic respiratory disease.(Bloom BM1 2014) These studies also accepted that the pO2 values were not of an acceptable level of agreement between venous and arterial(Byrne AL1 2014) The patients included in these meta-analysis were adult hospital patients predominantly from emergency departments but also includes intensive care patient, trauma units, cardiothoracic surgery patients and patients specifically with exacerbation of COPD. Table 1.1 below summarises the findings of these meta-analysis.

Parameter, Study	**Number of studies included**	**Mean difference compared to arterial**	**Lower 95% LOA**	**Upper 95% LOA**
pH				
Bloom	13	-0.033	-0.039	0.027
Byrne	18	-0.03	-0.023	0.090
pO_2 (kPa)				
Bloom	Not Included	-	-	-
Byrne	11	4.91	3.62	6.21
pCO_2(kPa)				
Bloom	12	0.589	-2.71	3.42
Byrne	18	0.553	-1.43	0.31
Bicarbonate (mmol/L)				
Bloom	10	1.03	-7.1	10
Byrne	Not included	-	-	-

Table 1. 1 Results of meta-analysis comparing arterial and venous blood gas results

Capillary blood from an ear lobe arterialised blood sample is now commonly used in respiratory clinics for determination of pH, pO2 and pCO2 to help guide clinical practice. This practice has been guided by a large meta-analysis of 29 studies (each of which included 664 to 222 samples per study) comparing paired capillary blood samples from an ear lobe and finger prick test to an arterial blood gas taken from taken from the radial artery. The meta-

analysis concluded that ear lobe sampling was 2.5 times more accurate in predicting arterial pO2 compared to a finger prick test. Both these capillary samples were generally more accurate at lower levels of pO2. The ear lobe samples were a good predictor of arterial pO2 (adjusted R2 = 0.88, mean bias = 0.507kPa) but finger prick samples were not (adjusted R^2 = 0.48, mean bias = 1.53kPa). The authors did not state what would be an acceptable level of mean bias or R^2 value. It covered a large range of pO2 values ranging from as low as approximately 3 kPa to 15kPa and a large diversity of population including adult and paediatric population in emergency department, critical care and outpatient environments. It also showed that both finger prick and ear lobe prick samples were accurate for assessing pH, with a mean bias of only 0.02. The range of values studied here was wide, including pH from 6.8 to 7.6. The study suggested that ear lobe prick was more accurate at assessing pCO2 but that both closely reflected arterial levels (with arterial versus earlobe adjusted r2 = 0.94, mean bias =0.253 kPa ; arterial versus fingertip, adjusted R^2 = 0.95, mean bias = 0.293 kPa). This study included patients with a wide range of pCO2 values, ranging from approximately 1.33kPa to 16kPa (Zavorsky GS1 2006). The summary of the result are given in table 1.2 below. A potential limitation of this study was the use of mean bias and R^2 values to form its conclusions, and more stringent tests can be applied, which will be discussed below.

Parameter, Type of capillary sample	Mean Bias	Adjusted R^2	Difference clinically significant?
pH Finger	0.02	0.9	No
Ear Lobe	0.02	0.94	No
pO2 (kPa) Finger	1.53	0.88	Yes
Ear Lobe	0.507	0.48	No
pCO2 (kPa) Finger	0.293	0.95	No
Ear Lobe	0.253	0.94	No

Table 1. 2 Summary of findings from the meta-analysis by Zvorsky comparing capillary blood gases to arterial

Similarly there have also been several studies in paediatric and neonatal populations which show good correlation of blood gases, apart from pO2, taken from capillary samples (normally taken from a heel prick in this patient group).(Yang KC 2002, Yildizdaş D 2004)(100) Two of these studies included paired results of patients on neonatal intensive care and two were from patients from paediatric intensive care units, including 33 to 116 patients. All showed good correlation between arterial and capillary pH and pCO_2 with $R^2>0.87$. However, these studies all focused on correlation only in their conclusions.

1.2.2 Electrolytes

Assessment of electrolytes is essential in patients who are acutely unwell. Having almost instant results from POCT could allow rapid treatment of life threatening emergencies or identification of patients who are at high risk of development of the potentially fatal complications of their derangement such as cardiac arrhythmias or seizures. It is unclear whether these tests are clinically reliable enough, however, to allow commencement of treatments or to monitor outcome.

There have been a number of studies that have compared electrolyte values between POCT blood gas analyser measurements with serum laboratory values. A study by Beggs in 2006 concluded there were no differences between arterial blood gas and venous laboratory samples for electrolytes when 238 paired samples were taken for sodium, potassium and chloride from intensive care patients. It showed strong correlation coefficients for sodium, potassium and chloride (0.945, 0.817 and 0.922).(A Beggs 2006). Subsequently other studies

have not replicated this level of correlation.(Campbell3 200, Anunaya Jain 2009, Binila Chacko 2011, Budak YU1 2012, Quinn LM1 2013). One study (Jain 2000) compared 200 paired ITU samples and showed only minimal differences between potassium (mean ABG potassium 3.74mmol/l (SD 1.92), mean serum potassium 3.896mmol/l (SD 1.848) ($p = 0.2679$)). However, the same study demonstrated differences in the testing modalities results for sodium (mean ABG sodium 131.28mmol/l (SD 7.33), mean serum sodium 136.45mmol/l (SD 6.50) ($p < 0.001$) with a correlation coefficient of 0.68.(Anunaya Jain 2009) A similar study by Quinn agreed with these conclusions but suggested that potassium arterial POCT values at lower concentrations (<3 mmol/l) did not show agreement to a clinically acceptable level with variation from serum samples between 1 and -0.3mmol/l (values within 95% confidence interval).(Binila Chacko 2011). Furthermore, a study published in 2013 concluded that potassium levels at higher concentrations (>5mmol/l) may also show a clinically relevant difference between sampling modalities (mean difference 0.44 mmol/l). This paper also differed in its conclusions regarding the accuracy of POCT sodium results, surmising that this was sufficiently accurate within the physiological range.(Quinn LM1 2013).

The reason for these differences in conclusions is not clear, however, the statistical analysis undertaken may provide some explanation. Quin et al, used a paired T-test. This approach does not analyse the range of results and so cannot provide a comparison to accepted accuracy measures as the analysis will only allow confirmation or rejection of the null hypotheses. Other studies have concluded that there wasn't sufficient concordance between POCT or venous results to support clinical care. Budak et al described a mean bias for potassium of -0.251 mmol/l with LOAs from -1.1 to + 0.597 and a mean sodium bias of -4.94 with LOAs of -10.05 to +0.97, both of which were considered too discordant to direct clinical decisions

(Budak YU1 2012). These results are similar to that of Jain et al 2009, however, there were discrepancies as to what each study defined as being a clinically acceptable difference. Both studies used the United States Clinical Laboratory Improvement Amendment (US CLIA) 2006, which accepts a difference of 0.5 mmol/l in measured potassium, and 4 mmol/l in measured sodium, from the gold standard measure of standard calibration solutions for their conclusions (Anunaya Jain 2009, Réminiac 2012). However, Budak et al 2012, argued that a difference of >0.25mmol/l in potassium should be considered clinically relevant but did not provide an adequate explanation for this cut off.

A further study described no clinically significant differences between whole arterial blood samples analysed in a POCT blood gas analyser compared to the serum venous values for several electrolytes including glucose, urea, sodium, potassium and creatinine, as shown in table 1.3, with 55-70 paired samples taken from patient in an adult intensive care unit of each.(Perkov 2006) This study was one of very few papers that covered a wide range of electrolytes rather than focussing on a small number of parameters.

Electrolyte	N	Mean Venous serum+/-SD	Mean Arterial POCT+/-SD	Difference in means
Glucose, mmol/L	55	7.14 +/- 1.62	7.17 +/- 1.68	0.03
Urea, mmol/L	55	11.96 +/- 8.39	13.87 +/- 10.75	1.94
Creatinine, mmol/L	55	156.26 +/- 137.93	154.20 +/-145.83	2.06
Potassium, mmol/L	70	4.28 +/- 0.46	4.23 +/- 0.47	0.05
Sodium, mmol/L	70	141.6+/- 17.03	138.8 +/- 5.69	2.8
Chloride, mmol/L	70	112.37 +/- 6.43	110.67 +/- 4.99	1.7

Table 1. 3 Comparison of Arterial POCT blood gas machine with Venous serum Lab analysed samples(Perkov 2006).

This study concluded the differences are clinically acceptable, however, did not comment how this conclusion was drawn nor on which standard references ranges this conclusion was based.

Table 1.4 below summarises the studies comparing samples assessed in a blood gas analyser to laboratory venous samples. These were taken from Intensive care and Emergency Department populations. It shows the lowest mean bias from the selected studies and the highest with the same applied to the LOAs

Parameter	Number of Studies Reviewed (patient number)	Mean Bias	Lower 95% LOA	Upper 95% LOA
Sodium (mmol/l)	5 (44-200)	1.77 to 5.17	-6.4 to-0.66	2.9 to 8.78
Potassium(mmol/l)	5 (44-200)	-0.3 to 0.156	-0.72 to -0.4	0.13 to 0.8

Table 1. 4 Arterial blood samples compared to venous laboratory samples (R King 2000, Anunaya Jain 2009, Binila Chacko 2011, Budak YU1 2012, Quinn LM1 2013)

There have been a number of studies assessing the accuracy of venous electrolytes as tested in a blood gas analyser to confirm the presence of DKA and acid base balance (Brandenburg MA1 1998, Menchine M1 2011). One study concluded that measurement of bicarbonate, pH, anion gap and glucose as a combined tool was sufficient to give a diagnosis of DKA with a sensitivity of 100% and specificity of 97.8%, however, the authors did not draw any conclusions of the reliability of the individual parameters when considered alone (Menchine M1 2011).

All of the above studies used arterial blood measured in a blood gas analyser compared to the venous laboratory test. There appear to be very few studies, which have used venous blood

analysed in a blood gas analyser for the same analysis. The only study found was taken in a paediatric intensive care population where 60 consecutive paired samples were taken and sodium and potassium were compared. This showed mean differences of -8.76mmol/l for sodium and -0.75mmol/l for potassium with 95% limits of agreement of -20.7mmol/l to 3.2mmol/l for sodium and -1.9 to 0.4 for potassium. They concluded that these were not clinically acceptable differences as they exceeded the recommended ranges as provided by the United States Clinical Laboratory Improvement Amendment (US CLIA) (Kumar. 2013). This is the laboratory regulation service regulated by the Centre for Medicare and Medicaid Services in the United States who's objective is to ensure quality laboratory testing (Medicaid 2016).

Another method for measurement of electrolytes is using an i-STAT portable analyser. This is a hand held battery powered analyser that uses disposable cartridges that can perform several analyses simultaneously with results available in 2 minutes. There is one cartridge that measures electrolytes including sodium, potassium, chloride, urea and glucose, measures packed cell volume and calculates Hb from this. Another cartridge measures blood gases. A study by Papadeain in a paediatric population including 225 samples attempted to assess the accuracy of this method and concluded that concordance between all electrolytes measured, as well as pH, was acceptable with a coefficient of variation (CV) of less than 2%. However, the concordance between creatinine and haematocrit values was lower (CV<9.5%). The authors used whole blood with samples taken in capillary tubes or blood gas syringes (the actual sites were not specified) from patients less than 3 months old and greater than 3 months old. Parameters were compared using coefficient of the variance, which is a potential limitation of this study as it is not the gold standard for comparing such variables(J. Martin Bland 1986)

(methods for comparing variable will be discussed later, (see section 1.3). It is unclear if these results are generalizable to an adult population but there are methodological differences which might limit comparisons. The standard method for measurement of electrolytes in adults uses serum samples whereas whole blood samples were utilised in this study (Christine Papadea1 2002).

A study in an adult population compared arterial blood measured in the istat analyser to central lab samples and gave correlation co-efficient values of 0.85 for Ca, 1 for K, 0.86 for Na, 0.99 and concluded it had suitable reliability for most clinical setting(Schneider J1 1997). This study again only used arterial blood drawn so might not be generalizable to most blood samples taken in a hospital setting nor acceptable as a means to gain serial samples from many patients.

Another study (Wilding 1993) compared venous samples measured in the Istat analyser to laboratory values using samples taken from 142 patients in Emergency Department and Outpatient areas. The authors reported Pearson's correlation coefficient (r) values with mean differences of 0.937 and 1.37mmol/l for sodium; 0.993 and 0.08mmol/l for potassium,; 0.904 and 1.00mmol/l for chloride, 0.996 and -0.22mmol/l for urea nitrogen; and 0.952 and 0.01mmol/l for glucose, respectively. This showed concordance of measurements and further analysis using linear regression also suggested favourable accuracy for this POCT measure. A limitation for this study was that the analysis did not include Bland-Altman plots or limits of agreement analysis (the recognised gold standards for comparing tests, which will be discussed fully in section 1.3) to enable the results to be more widely interpreted. This study

also compared the concordance between the i-stat analyser and the standard laboratory analyser when the analysis was done by laboratory staff using the analyser in the central laboratory compared to nursing staff working in the areas at the patient bedside and showed no clinically significant differences between these methods, however, the study did not state what a clinically significant difference would be. This interpretation included regression analysis which showed good levels of correlation ($r>0.95$) (Wilding 1993). Other studies have shown similar levels of accuracy. One such study by Mock (Mock T 1995) which reported coefficient of variation (CV) showed CVs of less than 3.5% for all the above parameters, however, only used a small sample size (of 10-20 healthy volunteers).

Use of capillary electrolytes is common practice in paediatric medicine. There are few studies of capillary whole blood samples tested in a POCT blood gas analyser for electrolytes. One such study (Yang KC 2002) compared capillary samples and arterial samples analysed in a blood gas analyser and concluded that there was good correlation between the following parameters: hemoglobin, hematocrit, sodium, calcium, glucose, lactate and osmolality. Again, however these results compared just whole blood samples taken through a blood gas analyser in neonates and did not compare them to gold standard laboratory values, so are of limited use in current adult medical practice.

Ionised calcium can be reported from most blood gas analysers. Ionised calcium is the physiologically active state of the ion as much of the total blood calcium will be bound by albumin and other blood proteins. Measurement of corrected total body calcium alone may not be a true reflection of the ionised calcium in patients who are unwell as other factors can

increase or decrease its protein binding e.g. acid/base disturbance or when albumin is very low. In these clinical settings ionised calcium may be of relevance and was commonly obtained via an arterial sample and processed via a blood gas analyser. Bilkovski et al. showed that there was concordance between arterial and venous samples processed in the same way with a correlation coefficient of r=0.94 (P<.0001) and a mean difference between venous and arterial ionized calcium measurements of 0.015mmol/l±0.045 (standard error) (P=.001)(R.N. Bilkovski 2004). This difference is likely to be of minimal clinical significance. Both of these samples use whole blood measurements and there is evidence that whole blood samples differ from serum for ionised calcium samples and will give a lower level by an average of 0.126 mmol/l, with the difference decreasing with lower values of ionised calcium (Seok Hui Kang 2014). The Clinical Laboratory Standards Institute (CLSI) suggests that both methods are acceptable (Sachs C 1991) , however interpretation at very low calcium values should be done with caution and serum samples requested if required.

1.2.3 Lactate

Lactate is a produce of anaerobic respiration, which occurs in many tissues when there is reduction in delivery of oxygen and so is a good indicator of organ perfusion in conditions such as sepsis or when patients are in shock.

Lactate is a common parameter checked on POCT analysers. As with blood gases the gold standard for analysis has been an ABG. This has led to studies assessing the concordance between an Arterial and venous POCT lactate analysis. One study (Ikami A 2013) which included samples from 72 emergency department patients with a range of lactate values from 0.5-14.6mmol/l, concluded that there was a high level of correlation showing variation from -

0.4 to +1.1 and a mean difference of 0.268mmol/l with venous levels being consistently higher to allow a correction with the formula below devised from regression analysis modelling:

$$\text{Arterial lactate (mmol/L)} = -0.259 + \text{venous lactate (mmol/L)} \times 0.996$$

There have been several similar studies with the same conclusions (Réminiac 2012, Akira Mikami 2013) however, the majority of studies did not specifically select patients with lactates outside the normal range. This was addressed in a study by Bloom et al (2014) reviewing patients with high lactates to determine if a venous blood sample can be used to accurately diagnose a lactic acidosis. This study showed the mean difference and standard deviation between venous and arterial blood for all patients was 1.06 ± 1.30 mmol/L and stated that using a cut off of 2mmol/l and 4 mmol/l would incorrectly diagnose a lactic acidosis in 36.2% and 17.9%(B. Bloom 2014). With the cut off of 2 being of particular significant as this is where hyperlacticaemia is defined. (Kyle J Gunnerson 2015)

Table 1.5 below summarises the results from 4 studies with samples taken from patients presenting to an emergency department. They compare arterial lactate (the gold standard) to venous measured in a blood gas analyser.

Parameter	Number of Studies Reviewed (patient number)	Mean Bias	Adjusted R^2
Lactate (mmol/l)	4 (72-188)	0.268 to 0.4	0.96

Table 1. 5 Comparison of arterial to venous lactate (Gallagher E.John 1997, Réminiac 2012, Ikami A 2013, Talayero Gimenez De Azcarate M. 2013)

1.2.4 Glucose

Point of care glucose analysis using capillary glucose is a very well established method of blood glucose measurement by clinical staff and patients at home and in hospital. Generally this produces accurate results within the physiologically normal range but there is concern about their accuracy in the hypo and hyperglycaemic ranges(R Boyd 2005, Rebel A1 2006). One group compared the glucose meter readings to central laboratory analyser readings, for both hypoglycemic and hyperglycemic values, and showed the differences were greater than 10% in more than 61% of samples. Further to this, in the hypoglycemic range, differences were greater than 20%, 57% of the time (Khan AI 2006).

Both POCT glucose meter glucose and POCT glucose measured in a BGA were examined in a literature review of 21 articles (Inoue S 2013), where the agreement was assessed by the percentage of values within 20% of the laboratory plasma measurement (as per the international organisation for standardisation, IOS, Criteria). The proportion of non-agreement was 12.5% for BGA samples and 1.3 - 9.3% for capillary blood glucose meters. It also used a meta-analysis from 3 studies (912 samples) as a straight comparison of accuracy between glucose metre and BGA values. This showed BGA glucose to be more accurate compared to a capillary blood measured in a glucose metre, (odds ratio for non-agreement,

0.04; P < 0.001) but not significantly more accurate than arterial blood measured in a glucose metre (odds ratio for non-agreement, 0.17; P = 0.20) glucose metre. Suggesting that the type of blood i.e. capillary or arterial sampled is more important for the accuracy than the method of analysis when differentiating between BGA and glucose metre.

Two studies within this meta-analysis included limits of agreement comparing POCT BGA results to central laboratory results (Hoedemaekers CW1 2008, Stadlbauer V1 2011). The results of these are shown in the table below (table 1.6). Both of these studies used arterial and venous samples with no clear differentiation in critically ill and intensive care patients. Neither specifically selected patients outside of the normal glucose range so had few results in this area.

Parameter	Number of Studies Reviewed	Mean Bias	Lower 95% LOA	Upper 95% LOA
Glucose	2	-0.464 to 0.15	-1.24 to 0.946	0.102 to 0.94

Table 1. 6 BGA glucose compared to laboratory plasma glucose *(Stadlbauer V1, 2011, Hoedemaekers, 2008).*

1.2.5 Haemoglobin and Haematological Parameters.

Haemoglobin and haemoglobin derivatives are commonly measured and reported from blood gas analysers but other POCT measures are being used increasingly in transfusion medicine to provide rapid access for blood count results.

Haemoglobin is essential for carrying oxygen to tissues and organs via the circulatory system to enable aerobic respiration. Its levels can be reduced through haemorrhage as well as other haematological and non-haematological diseases. It is an essential measure in acutely unwell patients. Blood gas POCT analysers have been investigated for their accuracy and reliability in providing haemoglobin results. One such study compared 238 paired arterial samples processed through a blood gas analyser to venous laboratory results and showed a correlation co-efficient of 0.934. Another study compared 81 paired arterial blood gas analysed samples and arterial samples sent to the laboratory and showed minimal difference between the means (0.19g/dL) but commented that the 95% limits of agreement were large (− 10.9 to +14.7 g/l)(Campbell3 200). A further study showed similar results (mean difference Hb -4.3 g/l (95% CI = -11.0 to 2.4)(Ray JG 2002). These studies all compared arterial samples measured in a blood gas analyser compared to the standard venous measurement. There are no such studies comparing venous blood measured in a blood gas analyser compared in a similar fashion.

Table 1.7 shows the combined results from 4 studies all of which were taken from ITU populations where limits of agreement and mean bias were analysed.

Parameter	Number of Studies Reviewed (patient number)	Mean Bias	Lower 95% LOA	Upper 95% LOA
Haemoglobin (g/l)	4 (100-238)	-0.433 to 0.91	-1.1 to -1.47	2.4 to14.7

Table 1. 7 Comparison of BGA haemoglobin to laboratory values (R King 2000, Ray JG 2002, A Beggs 2006, Quinn LM1 2013)

Despite not specifying guidelines to assess parity of results, all of the studies concluded that BGA haemoglobin lacked the required accuracy required to guide clinical care.

Haemocue is one of the most frequently used point of care analysers in transfusion medicine and haematology due to its accuracy with venous and arterial samples. There have been a number of studies which have confirmed this with values within 1g/dL (for 95% of samples) in multiple studies across a range of haemoglobin concentrations(Lardi A. M. 1998, J 2002, Rechner I. J. 2002, Sanchis-Gomar 2013). There have been some concerns about its reliability when capillary samples are taken and several studies have concluded that this method is not significantly accurate to guide patient treatment and requirement for transfusion.(Seguin P1 2010, Mimoz O1 2011, Sanchis-Gomar 2013) The mean difference (bias) between capillary haemocue and laboratory Hb was 0.2 g/dL (95%CI, 0.1;0.3), and limits of agreement were -1.3 g/dL (95%CI, -1.4;-1.2) to 1.7 g/dL (95%CI, 1.6;1.9), however, the discrepancies between capillary and lab samples were greater than 1 g/dL in 30.8% of cases.(Seguin P1 2010).

A study by Gehring, which examined and compared several POCT methods for HB measurement for 50 post operative ITU patients showed a mean bias of 0.2 g/dL for blood gas analyser Hb and 0.3 for haemocue compared to lab gold standard values(H. Gehring1 2002), suggesting parity.

INR is a common blood test taken to assess patients' coagulation especially in patients on vitamin K antagonists such as warfarin to assess whether it is within the therapeutic range. If

the INR is too high patients risk sustaining potentially life threatening haemorrhage. If it is too low then it will not be having its therapeutic effect. Point of care testing is now also widely used for measurement of INR. This enables health care works to quickly assess INR and advise on dosing of an anticoagulant within a clinic visit but also enables patients to monitor their own INR at home and adjust their dosing accordingly themselves. There have been many studies that have assessed the accuracy these meters. A literature review of 22 papers in 2012 concluded that they were sufficiently accurate for clinical use, however, their accuracy should be viewed in the context of the inherent inaccuracies in INR measurements. This is because there is a variability in laboratory measurements of INR with the coefficient of the variance (CV) in the order of 5% due to differences in reagent coagulometer combinations.(Christensen TD1 2012) One study in children, included in this review, compared POCT samples taken at 2 different time points to laboratory samples and showed Bland-Altman's 95% limits of agreement were 0.11 (-0.20; 0.42) and 0.13 (-0.22; 0.48).49 A study comparing the accuracy of patients using the POCT INR meter themselves with a laboratory INR value taken within one hour of the POCT test showed similar accuracy with a mean difference of 0.08 with 94% of readings within 0.5, 6 % from 0.5-1 and with no readings >1 unit from the laboratory samples.(M. NAGLER1 2013)

1.3 Statistical analysis for assessing the agreement between 2 methods of clinical measurement

There have been a number of different methods utilised in the papers reviewed above which compare a method of POCT to the gold standard tests. These include simple comparisons of the means, calculating the mean differences between the POCT test and the gold standard

tests, calculating the correlation coefficient, the coefficient of determination and using bland-altman plots, which include determining 95% limits of agreement.

The bland-altman plot method has now become the most commonly used method for this type of analysis and was used in 85 % of studies reported from 2007 to 2009 as opposed to the correlation coefficient, which is still used in 27% of studies (Rafdzah Zaki 2012).

The bland-altman method overcomes some intrinsic issues that are present when a correlation coefficient is used in isolation. A correlation coefficient will show a perfect correlation as long as there is a direct linear relationship between two parameters, despite the fact that there may be very poor agreement (Altman DG 1983) For example a test could show a value which is always twice as much as a gold standard test; this would show a perfect correlation between the two tests, however the agreement between the two would be poor. Similarly using regression analysis and a coefficient of determination only would not give a true measure of agreement as these are based on correlations rather than agreement.

1.4 Evidence for POCT improving patient outcomes and providing economic benefits.

The accuracy of POCT is of importance during clinical use, however, for it to be established as a viable method for patient assessment, POCT regimes need to demonstrate clinical efficacy. It is important to ascertain whether a quickly available result would improve patient outcomes in comparison with a slower laboratory processed sample. An example of this might

be by reducing morbidity or mortality or reducing patient length of stay in a department or hospital. POCT also needs to be shown to be cost effective if it is to be introduced widely, especially in the current time of financial austerity where there is high scrutiny on healthcare budgets.

A review by Lewandrowski highlighted decreased length of stay in the Emergency Department for patients who had point of care tests for a number of different presenting conditions.(Elizabeth Lee Lewandrowski1 2013). However, a large multicentre randomised control trial (1132 patients) did not replicate these results and described a decreased median length of stay when this method is used but no change in mean length of stay as well as being calculated to be less cost effective when compared to standard methods calculated by mean costs and quality-adjusted life-years (QALYs), and then estimated the probability of cost-effectiveness assuming willingness to pay £20,000 per QALY gained. The number of major adverse events defined by death, non-fatal AMI, life-threatening arrhythmias or hospitalisation for MI showed no significant increase in the POCT group.(Goodacre S1 2011)

A randomised control study at a large teaching hospital Emergency Department attempted to measure the extent to which point of care testing resulted in differences in clinical outcome for patients when compared with patients whose samples were tested by the hospital laboratory. This recruited 1728 patients who were randomised to point of care testing with an i-STAT system for blood analysis and to standard laboratory analysis. It then compared the outcome of the 2 groups and concluded that POCT brought faster changes in treatment for which timing was considered to be critical in 7% and influenced the treatment in 14% of cases

but that these patients did not spend less time in the department. Decisions were made 74 minutes earlier for haematological tests and 86 minutes earlier for biochemical tests. It also stated that the reduction in the time for the test results to be available did not seem to improve the clinical outcome of the patients. The other clinical outcomes measured were mortality, length of stay, the admission rates, the amount of time the patients spent in the department. The assessment of time critical in this paper was done by consultants and senior registrars using a visual analogue scale so objective measures were not used.(Jason Kendall 1998, Kendall JM1 1998)

A similar study (CURTIS A. PARVIN 1996) using the i-Stat device (measuring Na, K, Cl, glucose and blood urea nitrogeon), which compared 2 separate control periods over a few weeks with an experimental period where the i-Stat device was used also showed no difference in overall length of stay in the Emergency department in the included 4985 patients. Again suggesting that awaiting blood results does not have a large impact on length of stay.

Measurement of the precise economic benefit of point of care testing can be very challenging. It is easy to focus on the individual unit costs and without the benefit of economies of scale and automation then POCT is often more expensive than its laboratory alternative in this area. There have been a number of papers that have included formal cost effective analysis(Andrew St John1 2013). One of these looked at self glucose monitoring and found that self-care using POCT glucose monitor was of higher cost (additional £92) without providing clinically significant differences in outcomes such as HbA1C(Simon J 2008) Another article looked at

the cost of cardiac biomarkers and also concluded that this method is likely to produce higher ED costs, coronary care cost as well as cardiac intervention costs due to more frequent requirement of cardiac interventions, coronary care and intensive care admissions in the POCT group. This study did not assess clinical outcomes(Fitzgerald P 2011).

A paper by Kendal et al looked at the financial implications of using POCT as either a supplement to the standard laboratory test or a replacement in both Accident and emergency departments and intensive care. It concluded that the average cost per test was £4.06 with the laboratory arrangements but could be reduced to £3.78 per POCT method. This would give overall hospital savings from £8332-£20,000 if POCT replaced this method but there would be a substantial increased expenditure if it was used as a supplement only.(Kendall JM1 1999) In a similar study there was only a slight increased cost observed in the use of capillary blood glucose POCT measurement. Given the ease of performing and the immediacy of it results it is clear then how this has become the most frequently used method for glucose monitoring.(Lee-Lewandrowski E1 1994)

1.5 The challenges with venepuncture and other methods of blood sampling

The most common procedure performed in hospital for blood collection is venepuncture. Venepuncture is associated with pain and for a large proportion of people causes significant symptoms of anxiety and in some patients causes vasovagal reactions.(Langham BT 1993, Pavlin DJ 1993) This can effect patients ability to receive medically essential treatment if for

these reasons the refuse the tests.(Deacon B 2006) Venepuncture also has the possible complication of damage to the nerves in the arm or hand very occasionally causing a complex pain syndrome. This nerve damage is thought to be rare and incidence rates have not been reported, however due to the affected nerves being sensory it is likely to be underreported (Foad Elahi 2014). It can cause bleeding and bruising if the vessels are damaged (Yuan R.T.W. 1985, Yamada K. 2008). Arterial blood sampling is an alternative method of blood sampling but as discussed above this is associated with more severe pain as well as potential devastating complications such as ischaemia of the hand (Mortensen 1967). This complication, however, is more associated with arterial catheterisation, where the incidence of arterial occlusion is 0.09% (Clinical review: Complications and risk factors of peripheral arterial catheters used for haemodynamic monitoring in anaesthesia and intensive care medicine) rather than single arterial puncture.

Patients often undergo at least daily venepuncture in hospital. A study which assessed blood volumes taken during phlebotomy showed an average of 115 blood tests taken per patient in patients undergoing cardiac surgery, with blood gas analysis being the most frequent. This equated to blood volumes of 332mls in intensive care patients and 118mls in patients outside intensive care (Koch CG1 2015). This frequent venepuncture can cause veins to become thrombosed or scarred leading to decreased flow through these vessels to the point when venepuncture is no longer successful, which can happen to multiple veins, which are accessible for venepuncture leading to the patients having no accessible veins for peripheral cannulation. In turn this can lead to patients needing multiple attempts by clinical staff but may also require patients to be switched to often less effective oral medications when veins are not accessible. The alternative is to have more invasive central line insertions, where a larger intravenous line is inserted into the groin or neck, which has associated procedural risks

including infection, bleeding and pneumothorax (lung puncture) or PICC (peripherally inserted central catheter) lines which may be limited by the same problems of venepuncture above but can also become clotted preventing blood collection. Obesity and oedema can also limit ability to access veins due to difficulty visualising or palpating veins.(Cleveland-Noriega D.S. 2010) The relatively large blood volumes required in venepuncture may also contribute to anaemia or the requirement of red cell or other blood product transfusion (Koch CG1 2015)

Patients with certain conditions in hospital can require even more frequent blood tests to evaluate their on-going management. These include DKA patients where blood tests for pH, bicarbonate and potassium are required initially every 2 hours according to the current guidelines as stated by the JBDS (Group 2014). This is in addition to the hourly capillary blood glucose and ketone monitoring required for these patients. In this case if the capillary assessed parameters measured on a blood gas machine were deemed to be accurate, then this could be done at the same time using the same puncture when the blood sugar and capillary sample are taken. This then this could save the patient numerous blood tests at the same time as conserving the veins of patients who often need at least 2 intravenous cannulas in place to administer their fluid and insulin regimens.(Group 2014)

1.6 Conclusions

Serial blood tests are frequently required as part of guideline driven management of many common conditions including diabetic emergencies. Laboratory processing can be slow, delaying clinical care. Furthermore, serial testing is unacceptable to some patients and practically difficult in others (who suffer from poor venous access).

Point of care testing produces results more rapidly, which may facilitate care by allowing timely biochemical monitoring of acutely unwell patients, allow quicker triage of at risk patients and allow more rapid discharge of patients who are low risk. However, several studies have shown no differences in outcomes such as length of stay when this method is used, although few studies have assessed more complex outcomes such as changes in treatment practice or critical decision times. It is also unclear whether POCT is cost effective.

Many studies have compared POCT to laboratory processed venous blood samples. The use of POCT in these studies seeks to overcome the delay inherent in laboratory assessments, however the procedure of venesection is the same for the patient and remains painful and unpleasant when required serially. There is evidence in some biological POCT tests that a capillary sample may provide as a robust assessment as a venous sample. Capillary sampling has many potential advantages; it is reputed to be less painful, can be performed on many sites in rotation and would not impact on the availability of venous access points for future care. However, few comparative studies have been conducted in an adult population, and fewer still in an acutely unwell adult population. It would be important to determine the accuracy, reliability and acceptability of POCT using capillary samples in an acutely unwell adult population where serial blood tests are required for close monitoring purposes.

1.6.1 Blood Gases

Venous blood gases appear accurate enough to assess pH and bicarbonate. They cannot be used to accurately assess pO_2 or pCO_2, however, can be used to rule out significant hypercapnic respiratory disease. This has been evaluated by several high quality studies

including 2 meta-analysis with high patient numbers producing similar results and the same conclusions.

Capillary blood taken from arterialised ear lobe samples are accurate for assessing arterial pO2 especially at lower levels of pO2. They can also be used to assess pH, pCO_2 and bicarbonate. Finger prick capillary samples are similarly accurate in these parameters but cannot be used to reliably estimate arterial pO2. These results come from good quality meta-analysis by Zavorski. Due to their concerns with regard to bias, Bland-Altman 95% limits of agreement analysis was not undertaken. This analysis, however, could have been useful for individual clinicians to interpret the accuracy of these tests rather than basing conclusions around the coefficient of determination. This does not allow easy interpretation of how close this test is likely to be to the gold standard measurement and how likely it is to fall out of a range which is clinically acceptable.

1.6.2 Electrolytes

Arterial potassium measurement through a blood gas analyser is generally accurate but may not be accurate at lower concentration i.e. <3mmol/l, arterial sodium may show poor clinical correlation compared to serum samples.

These conclusions come from several individual studies that appeared appropriately powered in terms of patient numbers. Different methods of statistical analysis have been used for these studies. The better quality studies have incorporate limits of agreement and compare these to defined guidelines of acceptable accuracy (e.g. US CLIA). Where this has been done

potassium values are within the 0.5mmol/l limits, whereas sodium consistently falls short of the required 4mmol/l. The sample studied have predominately been arterial BGA samples and not venous. Further investigation in this area with pooled data, which included venous BGA compared to laboratory gold standards, would help with these conclusions.

There still appears to be conflicting evidence in the evaluation of electrolytes analysed in blood gas analysers outside of the normal physiological range when accurate testing is often more crucial. It may be useful to have good quality studies with conclusions based around Bland-Altman plots, which assesses accuracy over the range of values in adult populations to further assess this.

I-stat analysers are generally accurate for the assessment of sodium, potassium, chloride, urea and glucose using venous or arterial blood. This has been evaluated by several studies in the 1990s. These studies all focused on correlation rather than accuracy or assessment of coefficients of variation, again making a clinical interpretation of their accuracy difficult.

From the literature there does not appear to be any evidence with regards to the accuracy in the measurement of capillary blood samples in adults compared to standard testing when measured in blood gas analyser for glucose, electrolytes, haemoglobin or lactate. There is some evidence for the use of the i-stat analyser for measuring these parameters, however, capillary samples alone are not usually separated in these studies. I-stat analysers have lacked the ability to show significant benefits in patient care or economic benefits so this has led to this method of testing failing to become widely adopted in Emergency Care. Blood gas

analysers are present in most emergency care areas already, however, and the use of capillary testing using this method is unlikely to produce any significant increases in economic burdens for departments but could impact on the ability to closely monitor patients without the requirement and the problem of venous testing as discussed above.

1.6.3 Lactate

Venous lactate measured on a blood gas analyser shows good correlation and acceptable clinical accuracy. This has been evaluated by a number of studies across a range of lactate measurements. A possible correction formula has been devised, however, given the close correlation and relatively small mean difference many clinician may assess the trends rather than uses this adjustment. The diagnosis of a lactic acidosis may be overestimated when using a venous blood gas by up to 36.2 % according to one study (53). However, I think it could be argued that the arbitrary cut off for diagnosis of lactic acidosis may not be of great clinical significance and the correlation may be more useful.

Conclusions in these studies were based around mean bias and correlation again making an individual clinician uncertain about how likely the result of an individual test will fall outside an acceptable range. No acceptable ranges of agreement were proposed in these studies and do not appear to be present within the literature. The surviving sepsis campaign does not differentiate to whether arterial or venous lactate should be used and suggests any variety that is abnormal must be explained and uses a cut off of 4mmol/l as level suggestive of severe sepsis (Dellinger RP 2013). The upper normal limit is 2 mmol. For this study a cut off of

level of agreement is suggested at 0.5mmol/l which is similar to the lower limit of mean bias given in the studies above.

1.6.4 Glucose

POCT glucose machines are accurate in the normoglycaemic range, however, are less accurate at lower glucose concentrations. Arterial or venous samples measured through a blood gas analyser show good concordance in these ranges compared to venous serum laboratory values and maybe more appropriate when urgent assessment or verification is required. This has been well evaluated in a literature review of 21 articles with large patient numbers.

1.6.5 Haemoglobin and haematological parameters

Haemoglobin can be accurately assessed with haemocue point of care tests with arterial or venous samples (not capillary). There have been a number of high quality studies, which confirmed accuracy within the required 1.0g/dl for 95 % of values. Blood gas analyser arterial haemoglobin is less accurate but may be useful when very accurate measurement is not required. Several large studies have shown accuracies within 1.5g/dl for 95% of values. These studies do not explain the reasons for the required levels of accuracy and appear to use arbitrary cut offs. There does not appear to be clear guidelines in the literature for this, however, a separate study has stated "that transfusion of an erythrocyte concentrate (250 ml, cHb 250 g/l) increases the haemoglobin concentration of a patient by about 10 g/l, corresponding, for example, to a rise from 75 g/l to 85 g/l. Such a change should indeed be registered. Because of this, the confidence limits (±2 SD of the difference) for measured values of the instruments should lie within ±5 g/l." (Rajamäki 1980). This then seems like a

reasonable cut off. These studies all compared arterial samples measured in a blood gas analyser compared to the standard venous measurement. There does not appear to be good studies comparing venous blood measured in a blood gas analyser compared in the same way.

1.7 Hypothesis and Aims

1.7.1 Hypothesis

Capillary blood sampling will provide biochemical and haematological results that are accurate enough to guide clinical care when compared to the gold standard method of analysis, i.e. either a venous sample processed in NHS clinical laboratories or a venous sample processed in a blood gas analyser, in acutely unwell adults. Furthermore, capillary blood sampling will be more acceptable to patients than standard venous sampling.

1.7.2 Aims

We compared venous and capillary blood sample results (from a finger and earlobe) processed by a blood gas analyser to gold standard venous laboratory results in healthy controls and patients admitted to the clinical decisions unit in the Queen Elizabeth Hospital. We assessed if capillary POCT results for Na, K, Hb, Glucose and Lactate were sufficiently accurate compared with venous blood gas and laboratory processed results. Accuracy was determined by the criteria in table 1.6 for each criterion. We determined which sampling modality patients prefer using a visual analogue scale.

Parameter	Accuracy Measure	Guideline
Sodium	95% values within 4mmol/l	US CLIA
Potassium	95 % values within 0.5mmol/l	US CLIA
Haemoglobin	95% values within 0.5mmol/	Rajamäki A 1980
Glucose	95% values within 20%	JBDS, IOS
Lactate	95% values within 0.5	See section 1.6.3 above

Table 1. 8 Aims for the accuracy of the study parameters

2. Materials and methods

2.1 Ethics and Governance

This study was conducted according to the ethical principles set out in the Declaration of Helsinki (Rits 1964). All subject participation was supported by a favourable ethical review provided by the National Research Ethics Service Committee - West Midlands (NRES reference 14/WM/1057) and by sponsorship agreed by the University Hospital Birmingham NHS Foundation Trust (UHBFT) Research and Development Committee (See Appendices 1-2).

This study aimed to include patients with deranged biochemical parameters. Informed written consent was obtained from all participants prior to any research procedures in individuals with capacity to provide such consent. Delirium (defined as "an acute confusional state which is an organically-caused decline from a previously attained baseline level of cognitive function" (Gleason 2003)) is present in 14 – 56% of patients admitted with clinical conditions associated with abnormal blood biochemistry (Inouye 1994). It was recognised that some potential participants would not have capacity to provide fully informed consent at the time of recruitment due to delirium associated with their clinical condition.

As this study was intrusive research, requiring the collection of blood samples and clinical data, but not a clinical trial of an investigational medical product, the inclusion of these patients was governed the Mental Capacity Act. (Affairs 2005) Capacity to consent was determined by a senior physician prior to recruitment in all cases, as described in Section 3

and 30-33 of this Act. A potential participant was deemed not to have capacity where that person had "an impairment of or disturbance to the mind or brain and as a result is unable to

- Understand the information relevant to the decision
- Retain the information
- Use or weigh the information
- Communicate their decision" (Affairs 2005)

Approval was given to include adult patients without capacity as it was agreed that this research would specifically benefit patients with delirium secondary to deranged biochemical parameters by potentially improving care pathways without imposing a disproportionate burden and research of equal effectiveness could not be conducted if confined to patients with capacity (due to the incidence rates of delirium in this patient population at the time of admission).

For those participants unable to provide informed consent, informed assent was sought from the patient's personal consultee (PerCon) who may have been a relative, partner, carer or close friend. The PerCon was informed about the trial by a member of the research team and they were asked to give an opinion as to whether the patient should take part in the research, taking into consideration what the patient's wishes and feelings would be. If the PerCon decided that the patient would wish participate, they were asked give their Assent in writing.

This project required recruitment while biochemical parameters were deranged, and this was most common during the early phase of a patient's admission and treatment pathway. In some cases, it was not possible to identify a PersCon prior to potential recruitment. In these circumstances, specific permission was granted to include adult patients without capacity

following the assent of a Professional Consultee – an independent senior doctor involved in the care of the patient, under Section 32(9) of the Mental Capacity Act. As per section 33 of the Act, patients were not recruited or were immediately withdrawn from the study if the participant appeared to object to any study procedures or where the interests of the participant supported withdrawal.

2.2 Overall study design

This project was an open study with participants recruited from a single hospital based centre (UHB NHSFT, UK). The study had 3 parts. Validation (5 completed data sets), healthy volunteers (20 completed data sets) and acutely unwell diabetic patients with capillary blood sugars in the range of 10-15mmmol/L (20 completed data sets) and diabetic patients with capillary blood sugars in the range of >15mmol/L (20 completed data sets). Diabetic patients were chosen as these patients often also had deranged blood biochemistry (MS Elisaf 1996), evidence of lactic acidosis (Cox) and alterations in haemoglobin concentrations (Thomas 2004) and therefore provided a wide range of biological parameters to study.

2.3 Validation

Since there are no comparator studies of capillary sampling in adults it was not clear of the number of patients required to adequately power this study. This validation allowed assessment of feasibility of sampling and intra-patient variability, the latter allowed power calculations to ensure the patient study included sufficient numbers.

2.3.1 Participants

Healthy adults were recruited from an advertisement campaign in the Queen Elizabeth Hospital Birmingham and University of Birmingham campus. Subjects were screened against the inclusion and exclusion criteria (see table 2.1 and 2.2) and if the criteria were satisfied participants were consented and recruited. Participants were recruited to allow 5 completed data sets for the validation stage of the study. Hypoglycaemic patient were not included in the study as carrying out the 4 methods of blood sampling would incur a time cost of 20-30 minutes, which was felt to be ethically inappropriate given their need for immediate care. During this time period the potential for irreversible neurological sequelae would negate the potential benefits of the intended study as POCT glucose meters are already validated for states of hypoglycaemia and existing protocol have been devised with this testing modality in mind.

Cohort	Inclusion Criteria
Healthy volunteers	Provision of signed informed consent Age Limit: Minimum 18 years old. No upper limit. Queen Elizabeth Hospital Staff Vital signs within the normal range No significant past medical history Not taking regular prescription medications Non-smokers
Diabetic Patients with a BM of 10-15 mmol/L and BM >15 mmo/L	Age Limit: Minimum 18 years old. No upper limit. Provision of signed informed consent or personal consultee POCT glucose meter results of 10-15mmol/L or >15mmol/L based on last recorded PICS result Confirmation of diabetes in the patients' medical notes

Table 2. 1 Inclusion criteria for healthy volunteers and diabetic

Cohort	Exclusion Criteria
Healthy volunteers	Unable to provide signed informed consent Age limit: Below 18 years old. Not Queen Elizabeth Hospital Staff Observations outside the normal range Significant past medical history Taking regular prescription medications Smokers
Diabetic Patients with a BM of 10-15 mmol/L and BM >15 mmo/L	Age limit: Below 18 years old. No documented diagnosis of diabetes in the patient's medical notes POCT glucose meter result of <10 mmol/L

Table 2. 2 Exclusion criteria for healthy volunteers and diabetic patients

Demographic details and physiological observations (Blood pressure, saturations, heart rate, respiratory rate, temperature, and capillary refill time) were taken. Venous blood samples were collected for processing in the NHS accredited hospital laboratories (the gold standard). The venous sample was also used for blood gas analysis and an ear lobe and finger prick capillary sample were taken. These samples were collected consecutively in alternating order on 5 adults on 3 occasions over 1 week. See figure 2.1 below.

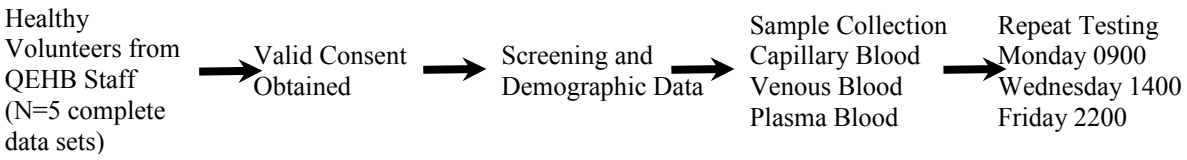


Figure 2. 1 Flow chart of validation study

2.3.2 Procedure for collecting the blood samples – Venous samples

Plasma venous blood gas samples and venous blood laboratory samples were obtained simultaneously through a single venepuncture site. A disposable latex free BD

VACUETTE® tourniquet was applied midway up the right arm of the non-dominant hand. The antecubital fossa was cleaned with a PDI Sani-Cloth CHG 2% disinfectant wipe for 30 seconds and the treated site allowed to dry for another 30 seconds. A 22G BD VACUTAINER® Safety-Lok™ butterfly needle was used to collect 2mls of venous blood gas sample into a Radiometer® PICO™ sampler followed by 2mls of venous blood plasma collected in a lithium heparin tube, 3mls in an EDTA tube and 3mls in a plasma serum gel tube (see figure 2.2).

Blood gas analysis was performed within 2 minutes using a point of care testing Cobas® b 221 blood gas analyser in the Clinical Decisions Unit or Emergency department of UHB and venous blood was sent to the UHB laboratory service for analysis; cell counts and biochemical analysis were performed in the Haematology and Biochemistry Laboratory at the Queen Elizabeth Hospital, Birmingham. Laboratory samples were delivered using SDS ac3000 pneumatic tube system to avoid delay and were processed as per standard practice within University Hospital Birmingham laboratory procedure to reproduce usual clinical care. All laboratory tests were conducted in NHS approved laboratories or their maintained equipment by trained staff and met the standards required by good laboratory standards as set out by the Medicines and Healthcare products Regulatory Agency (MHRA) (Gov.uk 2016).

The Cobas® b 221 blood gas analyser is a bench top blood gas analyser that gives results within 2 minutes. This machine has 1 point calibration every hour and 2 point calibration every 12 hours. The performance data for the machines can be seen in appendix 3.

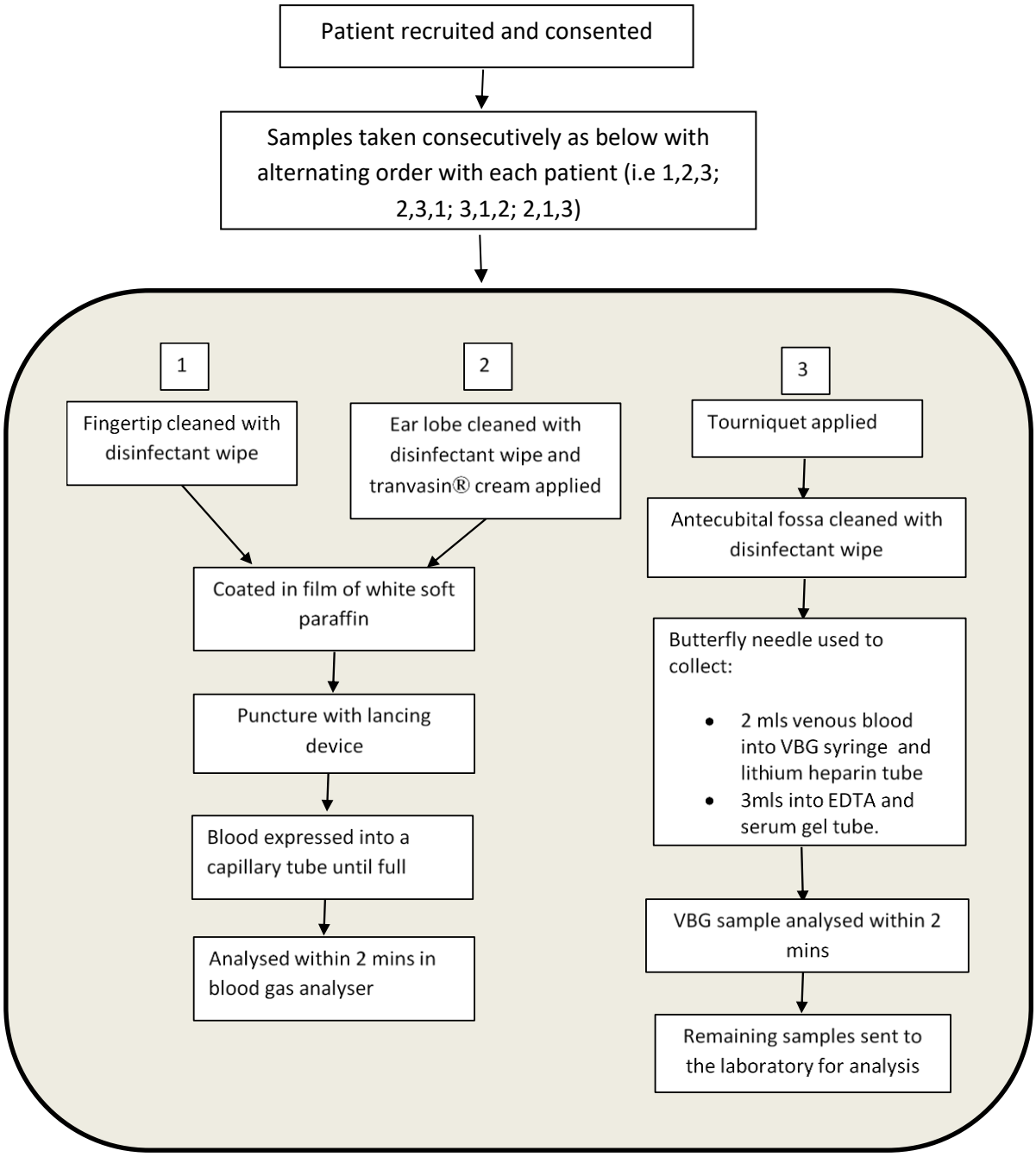


Figure 2. 2 Illustrating the blood taking procedure. The shaded area should be completed within 20 minutes

2.3.4 Ear and finger prick samples

The earlobe was cleaned with a PDI Sani-Cloth CHG 2% disinfectant wipe and the treated site was allowed to dry for 30 seconds. Following this a thin film of transvasin® cream was placed on the ear lobe to arterialise the ear lobe capillaries and left on for 10 minutes.

The earlobe was then cleaned again with the PDI Sani-Cloth CHG 2% disinfectant wipe for 30 seconds and the treated site was allowed to again dry for another 30 seconds. The ear lobe was then coated with a thin film of white soft paraffin prior to being punctured with a Unitstix® 3 lancing device and the earlobe gently squeezed until a drop of blood was expressed. A heparinised RAPIDLyte® Multicap-S plastic capillary tube was filled with a 150µl column of blood and closed at both ends with rubber caps as provided by the manufacturer. Blood gas analysis was performed immediately using a point of care testing Cobas® b 221 blood gas analyser at the Queen Elizabeth Hospital Birmingham. The same procedure occurred for the finger prick sample using the third or fourth finger of the non-dominant hand (See above figure 2.2).

2.3.5 Use of Transvasin Cream to collect earlobe samples

There was concern that the Transvasin cream itself may impact results due to the ingredients contained within it (although there is no evidence this cream alters capillary blood gas results including PaO2 and PaCo2) (Zavorsky 2006). In order to assess this, earlobe capillary samples collected both using and not using Transvasin cream were compared in 3 healthy volunteers prior to commencing the validation part of the study.

A small amount of Transvasin cream was applied to one earlobe on the anterior surface. Capillary blood was then taken using a lancet and capillary tube as described in 2.3.3 sequentially from the ear lobe without the Transvasin cream followed by the ear lobe with the Transvasin cream and then processed in the blood gas analyser and the results compared.

2.3.6 Sample size calculation

For the validation study, the results for intra-patient variability using co-efficient of variation and the relationship between samples were compared. The parameter with the highest variability would be predicted to have the highest sample number requirements so was used to ensure adequate sample numbers for all parameters being assessed.

Given the acceptability criteria described in section 2.4.2, sample size was based on the accuracy of the estimates of the percentages that were within 20% of the gold standard test. A previous study comparing blood glucose has suggested a sample size of 16 provides such power (R Boyd 2005).

2.4 Main Study

2.4.1 Healthy participants and acutely unwell subjects

A further 15 healthy patients (total 20) were recruited in the same way as 2.3.1 and were screened against the same inclusion and exclusion criteria (as per table 2.1 and 2.2). These participants had blood samples taken as per 2.2.2 and 2.2.3 on a single occasion only. The adult patients (20 diabetic patients with capillary blood sugars in the range of 10-15mmmol/L and 20 diabetic patients with capillary blood sugars in the range of >15mmol/L) were recruited following their acute admission to the Queen Elizabeth Hospital Clinical Decisions Unit. Suitable patients were identified from the Clinical Decisions Unit Prescribing

Information and Communications Service; an online database at QEHB that records patient's physiological parameters, laboratory datasets and medication prescribing and administration. These patients were then screened against the inclusion and exclusion criteria for diabetic patients (see table 2.1 and 2.2) and consented. Blood tests were taken as per 2.2.2 and 2.2.3. Subjects then scored their experience using a visual analogue score as described in section 2.4.2 below.

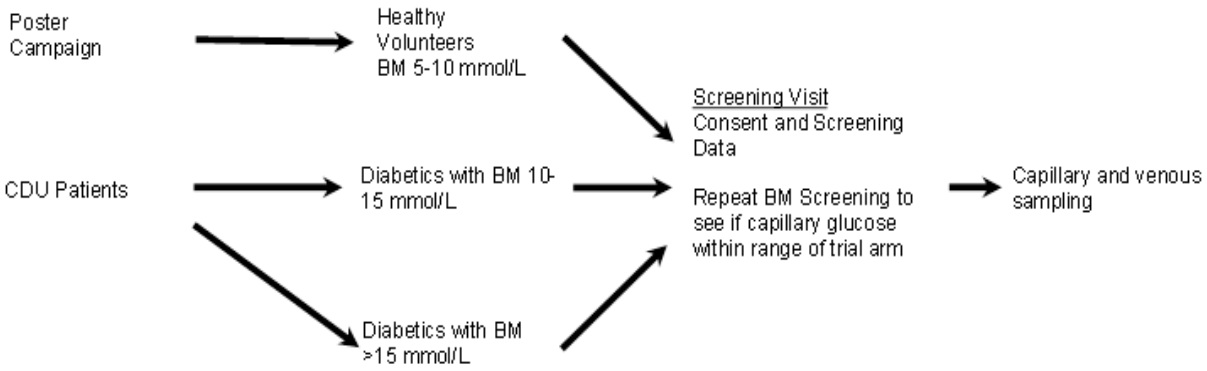


Figure 2. 3 Flow chart for healthy volunteers and acutely unwell adults

2.4.2 Acceptability criteria

As per the. section 1.7.2 of the introduction the acceptable level of accuracy were chosen using the criteria in table 2.3 below.

Parameter	Accuracy Measure	Guideline
Sodium	95% values within 4mmol/l	US CLIA
Potassium	95 % values within 0.5mmol/l	US CLIA
Haemoglobin	95% values within 0.5mmol/	Rajamäki A 1980
Glucose	95% values within 20%	JBDS, IOS
Lactate	95% values within 0.5mmol/l	See section 1.6.3 above

Table 2. 3 Acceptability Criteria

2.4.3 Experience rating

Each patient had their experience of the 3 methods of taking blood (ear lobe prick, finger prick and standard venepuncture) documented via a visual analogue scale for assessing pain (See figure 2.4). Given the perceived relatively low amount of pain for these procedure this was deemed most appropriate given it has been shown to be a sensitive measure of pain and is easy to use (Huskisson 1974). It has no formal validation as there is no gold standard for pain measurement and in fact other pain measures use this method for their own validation. (Huskisson 1974, A. Hawker 2011)

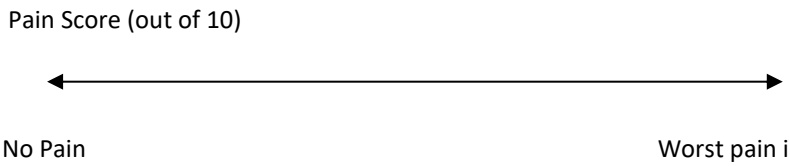


Figure 2. 4 Visual analogue pain scale used in patients' experience of the 3 different methods of blood taking.

2.5 Training for ear lobe prick

Prior to commencing the validation work for the study experience was gained in taking ear lobe capillary blood samples by a placement with the Home Oxygen Assessment Clinic at the Queen Elizabeth Hospital, Birmingham. This is the only area of the hospital currently which regularly uses capillary testing. Here, arterialization of the capillary blood occurs by first applying transvasin ® cream. This is a heat rub cream used in the symptomatic treatment of muscular pain which not only helps with arterialisation of the blood but also improves flow allowing successful collection via a capillary tube. This method of sampling had not yet been considered within our research protocol. During the feasibility assessment part of this study ear prick samples were initially trialed without the use of the Transvasin ® cream.

2.6 Statistical evaluation and sample size calculation

All statistical evaluation was conducted using SPSS Statistics (IBM, UK, Version 20) and Microsoft Excel (version 2012). Mean measurement error (ME) values for the three samples (venous blood, finger prick and earlobe sample) were assessed and the whether there was a significant difference between the groups determined using Friedman's test when there were more than one set of paired groups for comparison and Wilcoxon-signed ranks test when there was one. Post-hock analysis using Friedman's test pair wise comparisons was used when there was a significant difference between the sampling methods. Pearson's correlation coefficient was used to determine the degree of correlation of the finger and earlobe samples with the laboratory result.

To ensure adequate sample size in the patient group the first 6 patient samples were assessed. The parameter showing the highest variability as per the validation study was used to calculate sample size. This was calculated according to the mean and standard deviation of the percentage MEs in this group with a power of 95% and an α of 0.05 and will determine the number of participants required to detect 5% difference between the formal laboratory analysed blood test and the capillary blood test and so determine whether there is a statistically significant difference between these results. This was calculated for each sampling method i.e. finger prick, ear prick and venous BGA results.

A Bland- Altman plot was used to plot the difference between capillary derived and laboratory blood test result against the laboratory blood level. This plot provides a graphical

comparison of the level of agreement between two methods of assessment. As the procedure removes most of the variation between subjects and leaves the measurement error, it is expected that the differences will be normally distributed. This was tested using SPSS Statistics (IBM, UK, Version 20) using the Kolmogorov-Smirnov or Shapiro-Wilk test and also assessed using a Q-Q plot. A value of approximately less than 0.1 for the Kolmogorov-Smirnov test would suggest an approximate normal distribution. The Q-Q plot is a graphical method for comparing 2 variables and assessing theoretical distributions. Interpretation requires skill and assistance with this has been provided by an experienced statistician. When there is a high level of agreement, the mean measurement error (ME) (or mean bias) would be close to zero, and the limits of agreement of the MEs narrow.

To show whether there were statistically significant differences between the sampling methods as well as between the healthy and patient groups for the widths of the limits of agreement, an F test was used. This test calculates whether there is a significant difference between variance. As the widths of the limits of agreement are directly proportional to the standard deviation this test can be used to show whether the difference between these is statistically significant. A value of greater than 0.05 would show that there is no statistically significant difference in the widths of the limits of agreement.

When there is a pattern of correlation which is not equal across the range of values then linear regression analysis was used to model the distribution and allow estimates of the 95% prediction intervals (where 95% of the MEs are predicted to fall). This was done using the SPSS statistical software which can model the data and in doing so enabled predictions of the

mean ME for any given gold standard value including 95% prediction intervals. In doing so it enables a formula to be devised for any given gold standard value. When the results could not be modelled by linear regression and the results of normality testing did not fit an approximate normal distribution weighted average centile were calculated from SPSS to enable an assessment of the calculated limits of agreement.

It was predicted that the healthy control group may be different from the patient group for age given that they are selected from hospital staff who are within working age when compared with a patient group that included patients of any age acutely admitted to hospital. For this reason the results from each group were split into quintiles and mean bias calculated and compared. Statistical difference between the quintiles was then assessed using Kruskal Wallis test. If there was no significant difference across the quintiles then it is likely that age is not a significant factor when determining differences between sampling modalities tested and the gold standard.

Using the same assumptions of a normal distribution of MEs the proportion of patients within the acceptability criteria for each of the parameters were also calculated. Where a parameter, did not demonstrate a normal distribution for the MEs confidence interval were also included.

Analysis of the experience rating was done by calculating the median values for pain scores as well as the quartiles. Comparisons between the sampling modalities and between the healthy and patient groups was done using Friedman's analysis and post hoc analysis with Wilcoxon-signed ranks test.

3. Results

3.1 Validation: The use of Transvasin cream

Transvasin cream is used to increase blood vessel dilatation and thus enhance capillary sample collection in some centres. However, it was unclear if this might alter biochemistry readings or whether this was needed in the current study. To assess this a validation study was conducted to assess the impact of Transvasin cream use on blood parameters, which included 3 subject (see 2.3.4.).

3.1.1 Results of Transvasin Feasibility testing

Table 3.1 shows the absolute values and percentage difference in electrolytes between samples where Transvasin cream was used and where it was not been used prior to collecting capillary ear prick samples, in three subjects.

Participant	**1**			**2**			**3**		
Parameter	With TV	Without TV	% Difference	With TV	Without TV	% Difference	With TV	Without TV	% Difference
Sodium mmol/L	137.8	137.8	0	141.4	140.4	-0.71	139	136	-2.21
Potassium mmol/l	4.79	4.63	-3.46	4.31	4.27	-0.94	4.22	5.52	-30.1
Bicarbonate mmol/l	22.9	22.9	0	23.9	24.2	1.24	23.6	Insufficient	Insufficient

Ionised Calcium mmol/l	1.176	1.194	1.51	1.21	1.197	-1.09	1.188	1.192	0.34
Chloride mmol/l	104.3	103.7	-0.58	103	103.6	0.58	102.5	103.3	0.77
pH	7.426	7.41	-0.21	7.399	7.419	0.27	7.428	Insufficient	Insufficient

Table 3. 1 Comparison of electrolytes between capillary ear prick sample with and without Transvasin TV cream

Overall, the use of Transvasin cream greatly improved the technical ability to collect samples, by enhancing blood flow. There were difficulties in acquiring the required volume of blood from the 3rd participant when no Tranvasin was used, and so the dataset is incomplete. The first 2 participants demonstrate little intra-person variability between the electrolytes using the 2 sampling methods with a maximum of 4.22 % variation. However, there was a difference in potassium concentrations between the two sampling methods with the 3rd participant. This might reflect the technical difficulties experienced in collecting the sample, or the duration of the collection time.

It was considered necessary to use Transvasin cream for the collection of ear prick samples as it was deemed not feasible to gain the required volumes of blood without using this cream. Furthermore, the cream did not appear to cause significant differences in electrolyte concentrations, overall.

3.2 Validation study; Intra-patient variability

Participants were recruited to the validation study until 5 complete data sets were achieved. This resulted in a total of 8 participants recruited to this part of the study.

3.2.1 Population demographics for validation work

Table 3.2 below shows the demographics for participants involved in the validation study. These were healthy subjects recruited from hospital staff members.

	Healthy subjects
Number (n)	8
Age: Mean **Median** **Range**	32.8 28 24-49
Gender **Male** **Female**	 4 4

Table 3. 2 The demographic of the participants in the validation study

3.2.2 Validation results

Samples were collected consecutively in alternating order on 5 adults on 3 occasions over 1 week, as shown in figure 2.2 (methods). Tables 3.3a – 3.3d show the results of the validation study. Each table provides the mean of the 3 blood sample results for each sampling modality with the standard deviation (SD), and the coefficient of variation (CV) for each subject. Table 3.3a show the results for glucose. The median CV for the laboratory sample was 8.9% (IQR 7.9 – 10.5), the median CV for the finger prick sample was 12.6% (IQR; 11.4 – 18.0) and for the ear prick sample was 12.7% (IQR 9.3-20.3).

	Finger Prick			Ear Prick			Laboratory Result		
Participant	**Mean (mmol/l)**	**SD**	**CV (%)**	**Mean (mmol/l)**	**SD**	**CV (%)**	**Mean (mmol/l)**	**SD**	**CV (%)**
1	5.36	0.98	18.27	Incomplete data			4.46	0.57	12.97
2	Incomplete date			6.33	0.52	8.29	5.5	0.54	9.73
3	6.73	0.55	8.17	6.9	0.85	12.3	5.8	0.5	8.62
4	Incomplete Date			Incomplete Data			5.53	0.51	9.27
5	Incomplete Data			5.47	0.15	2.79	4.36	0.35	8.04

6	6.5	0.82	12.59	6.9	1.93	27.95	5.8	1.2	20.68
7	6.6	0.75	11.43	6.8	0.88	13.07	5.53	0.31	5.52
8	6.13	1.10	17.96	5.73	1.30	22.70	4.77	0.35	7.36

Table 3.3 a Result of the validation study for glucose. It shows the mean, standard deviation (SD) and coefficient of the variance (CV) of the 3 samples taken for each patient for the finger prick, ear prick and laboratory samples.

Table 3.3b show the results for sodium. The median CV for the laboratory sample was 0.6% (IQR 0.5– 0.8), the median CV for the finger prick sample was 0.8% (IQR; 0.5 – 0.8) and for the ear prick sample was 0.8% (IQR 0.5-0.8).

	Finger Prick			Ear Prick			Laboratory Result		
Participant	**Mean (mmol/l)**	**SD**	**CV (%)**	**Mean (mmol/l)**	**SD**	**CV (%)**	**Mean (mmol/l)**	**SD**	**CV (%)**
1	140.5	0.707	0.503	139.8	0.707	0.552	141.3	0.772	0.667
2	142.4	0.579	0.407	142.6	1.56	1.10	141.0	0.816	0.579
3	141.9	0.835	0.588	140.6	1.08	0.767	139.7	1.53	1.09
4	140.1	0.611	0.436	138.9	1.12	0.803	139.3	1.15	0.829
5	142.2	1.78	1.25	140.0	1.23	0.878	141.7	0.577	0.408
6	140.2	1.75	1.25	138.9	1.15	0.830	139.3	1.53	1.10
7	143.1	1.27	0.885	140.4	0.173	0.123	138.3	0.577	0.417
8	140.5	0.874	0.622	Incomplete data			140.2	0.902	0.643

Table 3.3 b. Result of the validation study for sodium. It shows the mean, standard deviation (SD) and coefficient of the variance (CV) of the 3 samples taken for each patient for the finger prick, ear prick and laboratory samples.

Table 3.3c show the results for potassium. The median CV for the laboratory sample was 5.6% (IQR 4.8– 7.3), the median CV for the finger prick sample was 5.5% (IQR; 4.8 – 6.7) and for the ear prick sample was 5.5% (IQR 3.6-6.0).

	Finger Prick			Ear Prick			Laboratory Result		
Participant	**Mean (mmol/l)**	**SD**	**CV (%)**	**Mean (mmol/l)**	**SD**	**CV (%)**	**Mean (mmol/l)**	**SD**	**CV (%)**
1	4.19	0.278	6.63	4.27	0.227	5.32	4.2	0.082	1.94
2	4.36	0.139	3.19	4.41	0.247	5.60	4.367	0.04	0.92
3	4.09	0.203	4.97	4.19	0.375	8.95	4.33	0.208	4.80
4	4.89	0.915	18.7	4.69	0.271	5.77	4.7	0.265	5.63
5	3.8	0.203	5.34	4.17	0.08	1.92	4.23	0.306	7.22
6	4.16	0.474	11.4	4.40	0.183	4.17	Incomplete data		
7	3.65	0.240	6.57	3.95	0.270	6.82	4	0.3	7.5
8	4.09	0.221	5.41	3.98	0.007	0.18	4.33	0.321	7.42

Table 3.3 c Result of the validation study for potassium. It shows the mean, standard deviation (SD) and coefficient of the variance (CV) of the 3 samples taken for each patient for the finger prick, ear prick and laboratory samples.

Table 3.3d show the results for haemoglobin. The median CV for the laboratory sample was 1.9% (IQR 1.0– 3.5), the median CV for the finger prick sample was 3.4% (IQR; 2.0 – 4.4) and for the ear prick sample was 3.2% (IQR 2.1-3.6).

	Finger Prick			Ear Prick			Laboratory Result		
Participant	**Mean (g/l)**	**SD**	**CV (%)**	**Mean (g/l)**	**SD**	**CV (%)**	**Mean (g/l)**	**SD**	**CV (%)**
1	Incomplete data			Incomplete data			135	2.83	2.10
2	Incomplete data			152.1	0.928	0.610	147	1.41	0.961
3	140.5	5.87	4.18	146.1	6.47	4.43	135.7	4.04	2.98
4	Incomplete data			155.8	5.05	3.24	144.7	0.577	0.399
5	151.8	7.65	5.04	147.8	5.36	3.62	144.7	5.03	3.48
6	154.8	2.99	1.93	Incomplete data			146.3	1.53	1.04
7	151.1	0.351	0.232	Incomplete data			138.3	1.53	1.10
8	145.5	6.54	4.50	137.7	2.89	2.1	136.	2.08	1.52

Table 3.3 d Result of the validation study for haemoglobin. It shows the mean, standard deviation (SD) and coefficient of the variance (CV) of the 3 samples taken for each patient for the finger prick, ear prick and laboratory samples.

These results show intra-patient variability was greatest in the glucose sampling with a co-efficient of variation up to 28% in the finger prick sample, 27% in the ear prick sample and 21% in the laboratory result. As this was higher than that of the sodium, potassium, and haemoglobin, this parameter was used to formulate the sample size calculation.

3.2.3 Sample size calculations

Sample size calculation was based on the first 6 patient group glucose results (as per the validation study). The mean difference for each sampling method was 4.18, 6.21 and 3.05 with standard deviations of 4.18, 8.31 and 4.06 for finger prick, ear prick and venous BGA

samples respectively. With an α of 0.1 and β of 0.05 this gives sample size estimations of 13, 23 and 23 for each sampling method. With the proposed combined total of 40 patients in the patient group this was therefore deemed adequate.

3.3 Participant Demographics

Table 3.3 below shows the demographics of the healthy participants and patient groups within the study.

	Healthy subjects	Diabetic subjects with blood glucose between 10 – 15 mmol/l	Diabetic subjects with blood glucose >15 mmol/l
Number (n)	23	25	23
Age in years:			
Mean	33	67	65
Range	24-49	37-87	19-84
Gender			
Male	9	13	14
Female	14	12	9
Ethnicity			
Caucasian	12	15	17
Asian	10	6	3
Afro-Caribbean	0	4	3
Other	1	0	0

Table 3. 3 Demographic date for healthy participants and acutely unwell patients

Figure 3.1 (below) shows a consort diagram outlining sample collection in all participants

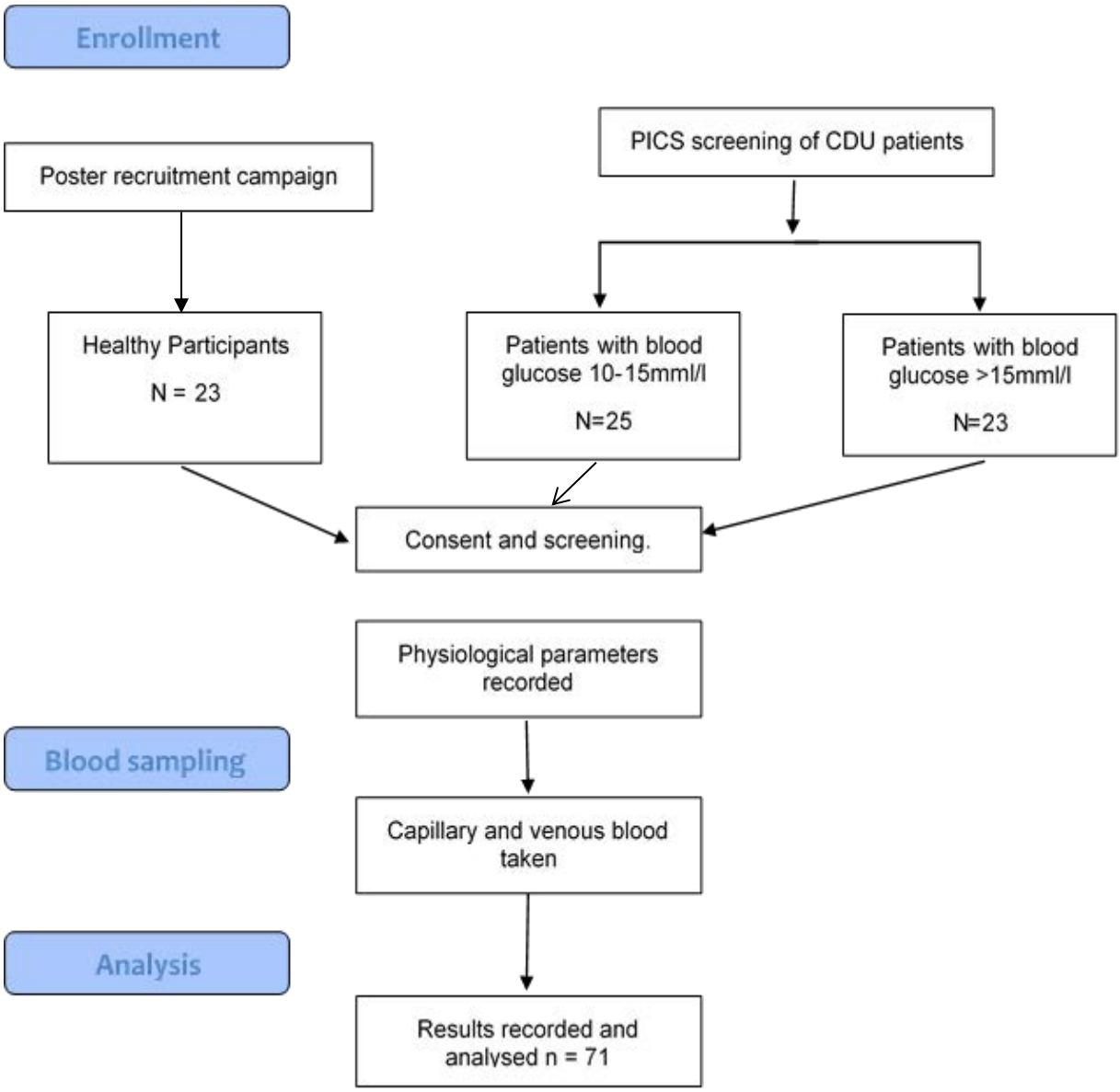


Figure 3. 1 Consort diagram outlining sample collection in all participants

3.4 Laboratory Parameters

Earlobe, finger prick and the venous blood sample analysed using the blood gas analyser (BGA) was compared with the gold standard laboratory processed samples. Data for each participant, sampling technique and parameter as well as admitting diagnosis for the patient

group are presented in appendices 4-5. Analysed data are presented for each parameter sequentially below.

3.4.1 Glucose

The acceptability criteria for glucose was that results should be within 20% of the gold standard plasma sample.

Table 3.6 -3.8 summarise the results from the glucose BGA results for the capillary finger prick, ear prick and venous samples compared to the gold standard venous plasma glucose laboratory result. The full results can be seen in appendix 1. Results have been divided into healthy participant, patient and the combined dataset. The mean measurement error (ME) or bias, standard deviation and the Bland-Altman 95 % limits of agreement (LOA), as well as the Pearson's correlation coefficient between the tested samples and laboratory samples have been calculated. Mean bias and LOA have also been calculated as a percentage of the plasma glucose level to allow comparison with the ISO guidelines.

Normality testing of the 3 methods was conducted to test whether the MEs were normally distributed so the calculations of the limits of agreement are valid. This has also been done for the percentage measurement error, as shown in table 3.4.

	Kolmogorov-Smirnov			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	Df	Sig.
FP	0.117	69	0.021	0.913	69	0
EP	0.272	60	0	0.426	60	0
VP	0.094	69	.200*	0.938	69	0.002
FP %	0.171	69	0	0.879	69	0
EP%	0.115	59	0.049	0.92	59	0.001
VP %	0.087	69	.200*	0.977	69	0.239

Table 3. 4 Normality testing of the MEs and percentage MEs between Finger Prick (FP), Ear Prick (EP) and Venous (VP) BGA glucose and standard laboratory values

When these results were compared to the Q-Q plot, there was an approximate normal distribution of the ME results for the finger prick and the venous prick as well as the ear prick and venous prick percentage measurement error, as the Kolmogorov-Smirnov result was approximately 0.1 or less and the Q-Q plot was in keeping with a normal distribution. However, ear prick MEs and finger prick percentage MEs did not equate to a normal distribution, as the Kolmogorov-Smirnov result was greater than 0.1 and the Q-Q plot was not in keeping with a normal distribution so assessment of these limits of agreement are not valid.

There were 6 incomplete data sets for the ear prick sample. A further sample was reported as out of range for the ear prick sample on the BGA with no value given and could not be included and 1 sample from each of the finger prick and ear prick groups could not be compared as a plasma sample was reported as not received by the laboratory staff. A further ear prick sample had one result that showed extreme variation from the laboratory sample (0.8mmol/l compared to plasma value of 19.6). This sample was difficult to collect and had a prolonged collection time. Analysis has included and excluded this result in order to demonstrate the effect of this outlier.

Table 3.5 below shows the results for the blood glucose finger prick samples. Both the patient groups demonstrated a strong correlation with a Pearson's correlation co-efficient (r) of 0.983 and 0.989 respectively. The healthy participant group did not show the same strength of correlation with an r of 0.566. The mean ME (bias) in the patient group was very

similar to the laboratory plasma sample of 0.208mmol/l (1.97% bias). The healthy participant group did not show this level of proximity with mean bias of 0.377 (7.74%). The limits of agreement of the MEs in the healthy participant group (where 95% of the differences values are predicted to fall) were within -1.43 to 2.18mmol/l of the plasma sample. This was a narrower range than the range for the patient group of -2.13 to 2.54, however when expressed as a percentage (as per the ISO guidelines) of the laboratory sample the healthy participant limits of agreement were much wider with limits of agreement ranging from -29.1% to 44.7% compared to the patient group -13.2 to 17.1%. The percentage MEs in this group as mentioned was not normally distributed so interpretations based on these would not be valid.

Participant group	Complete data set	Mean bias mmol/l / % bias	Standard Deviation of the MEs mmol/l (%)	Lower 95% LOA / (%)	Upper 95% LOA (%)	Pearson's Correlation co-efficient
Healthy Participants	22/23	0.377 (7.74%)	0.92 (18.8%)	-1.43 (-29.1%)	2.18 (44.7)	0.566
Diabetic patients	47/48	0.208 (1.97%)	1.19 (7.72)	-2.13 (-13.2)	2.54 (17.1)	0.983
Combined	69/71	0.26 (3.81%)	1.11 (12.5)	-1.91 (-20.8)	2.43 (28.4)	0.989

Table 3. 5 Results of finger prick glucose compared to venous laboratory plasma samples in healthy participant group, patient group and combined results.

Table 3.6 shows the results for the finger prick glucose samples compared to the plasma laboratory samples and have been analysed with and without the outlying sample as discussed above. When the outlier was removed, the correlation in the patient group and combined groups was strong with a Pearson's correlation co-efficient (PCC) of 0.978 and 0.987, respectively). Although still strong, the correlation was weaker in the healthy

participant group (0.724). When the outlying sample was included the correlation between finger prick and laboratory glucose results was weaker, with PCC for the patient and combined group of 0.833 and 0.978 respectively. The mean bias in each of the healthy participant, patient and combined groups (with or without the outlier) were not as close to the plasma glucose results as the finger prick samples, with values of 0.69 (13.3%) for the healthy group, 0.358 (6.93%) for the diabetic group with the outlier and 0.85 without. The limits of agreement for the ear prick MEs were not normally distributed as discussed above so are not valid. The MEs as percentages in this group, however were normally distributed and demonstrated quite weak correlations in the healthy group with LOA of -20.1% to 46.7%. This was improved in the patient group when the outlier was excluded with LOAs of -12.6 to 26.5 and the 2 groups combined -16.4 to 34.6%.

Participant group	Complete data set	Mean bias mmol/l (% bias)	Standard Deviation of the MEs mmol/l (%)	Lower 95% LOA mmol/l (%)	Upper 95% LOA mmol/l (%)	Correlation co-efficient
Healthy Participants	20/23	0.69 (13.3%)	0.863 (17%)	-1.00 (-20.1 %)	2.38 (46.7%)	0.724
Diabetic patients	40/48	0.358 (4.36%)	3.36 (9.97%)	-6.22 (-32.9%)	6.93 (41.6%)	0.833
Diabetic patients - without outlier result	39/48	0.85 (6.93%)	1.16 (9.97%)	-1.42 (-12.6%)	3.13 (26.5%)	0.978
Combined	60/71	0.46 (7.35%)	2.78 (18.8%)	-4.98 / -29.4%	5.91 (44%)	0.91
Combined - without outlier	59/71	0.8 (9.11%)	1.07 (13.0%)	-1.29 / -16.4%	2.89 (34.6%)	0.987

Table 3. 6 Results of Ear prick sampling compared to venous laboratory plasma samples in healthy participant group, patient group and combined results.

Table 3.7 describes the venous BGA glucose results compared to the venous plasma results. In concordance with all BGA samples the mean bias was consistently higher than the plasma samples in both groups with a mean bias of 0.282mmol/l (5.37%), 0.211mmol/l (2.12%) and 0.23mmol/l (3.15%) in the healthy, diabetic and combined groups respectively. The LOAs were also narrower than for the ear prick and finger prick at -1.19 to 1.75mmol/l (-22.2 to 33.1%) in the healthy participant group, -1.63 to 2.05 (-7.38 to 11.6%) in the patient group and -1.4 to 1.9 (-14 to 20.6%) with the groups combined. This was reflected by the strong correlation seen in both the diabetic and combined group both with PCCs of 0.993).

Participant group	Complete data set	Mean bias mmol/l (%)	Standard Deviation of the MEs mmol/l (%)	Lower 95% LOA (%)	Upper 95% LOA (%)	Correlation co-efficient
Healthy Participants	22/23	0.282 (5.37)	0.751 (14.1)	-1.19 (-22.3)	1.75 (33.1)	0.739
Diabetic patients	47/48	0.211 / (2.12)	0.940 (4.85)	-1.63 (-7.38)	2.05 (11.6)	0.993
Combined	69/71	0.23 (3.15)	0.879 (8.9%)	-1.4 (-14.0)	1.9 (20.6)	0.993

Table 3. 7 Results of Venous BGA glucose compared to venous laboratory plasma samples in healthy participant group, patient group and combined results.

Figure 3.2 – 3.4 are Bland-Altman plots that compare the finger prick differences compared to the laboratory plasma samples with combined patient and healthy participant followed by each of these individually. A graph showing a mean bias close to 0 with narrow limits of agreement lines would confer a comparable test. To assess this test against our aim of showing a glucose measurement within 20% of the laboratory samples for 95% of the values, a line showing the 20% limits is provided.

Figure 3.2 describes the finger prick glucose compared to the laboratory plasma glucose in healthy participants. Despite the mean difference being close to 0, the 95% limits of agreement were wide and within this normoglycaemic range (4.4-6.1mmol/l fasting) do not lie within the 20% of plasma values required by the ISO guidelines.

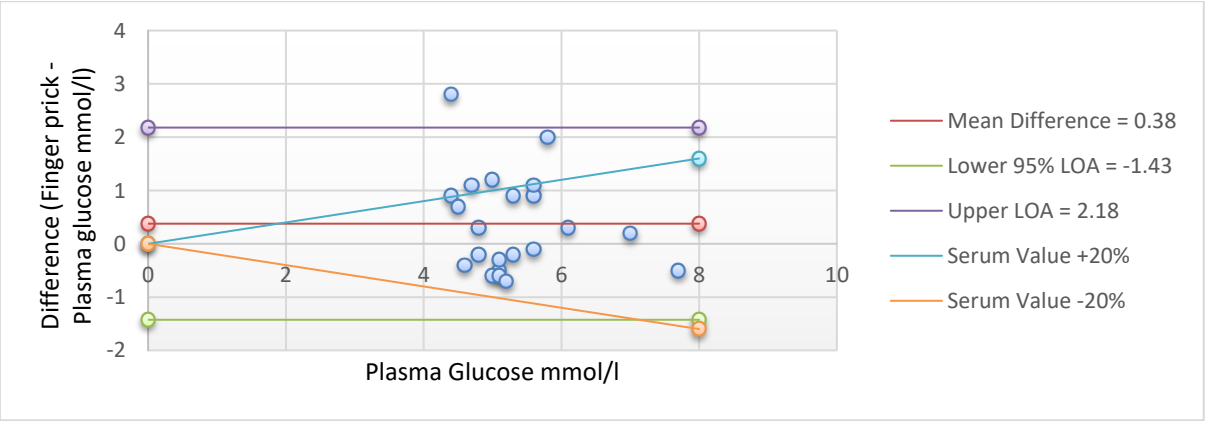


Figure 3. 2 Bland-Altman Plot for finger prick glucose BGA results compared to laboratory plasma glucose in Healthy participants

Figure 3.3 describes the Bland Altmann plots for finger prick glucose compared with the laboratory sample for the diabetic patient group. The mean difference was close to 0 and the 95% limits of agreement cross the required 20% of the plasma value in the hyperglycaemic range with all values above 10mmol/l being within 20% of the plasma value. The limits of agreement, however, cross at approximately 12mmol/l.

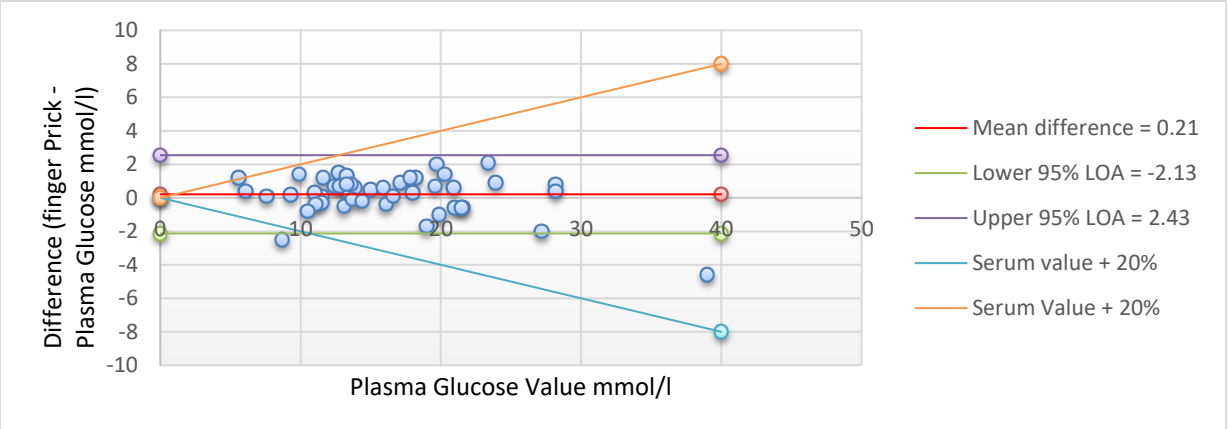


Figure 3. 3 Bland-Altman Plot for finger prick glucose BGA results compared to laboratory plasma glucose in acutely unwell diabetic patients

Figure 3.4 describes the combined results for all participants, comparing finger prick to laboratory glucose. Within the hyperglycaemic range (above 10mmol/l), the 95% limits of agreement approach the required accuracy of within 20% of the plasma value, however, within the normoglycaemic range many values do not satisfy this criteria. The mean bias remained slightly higher than the plasma value.

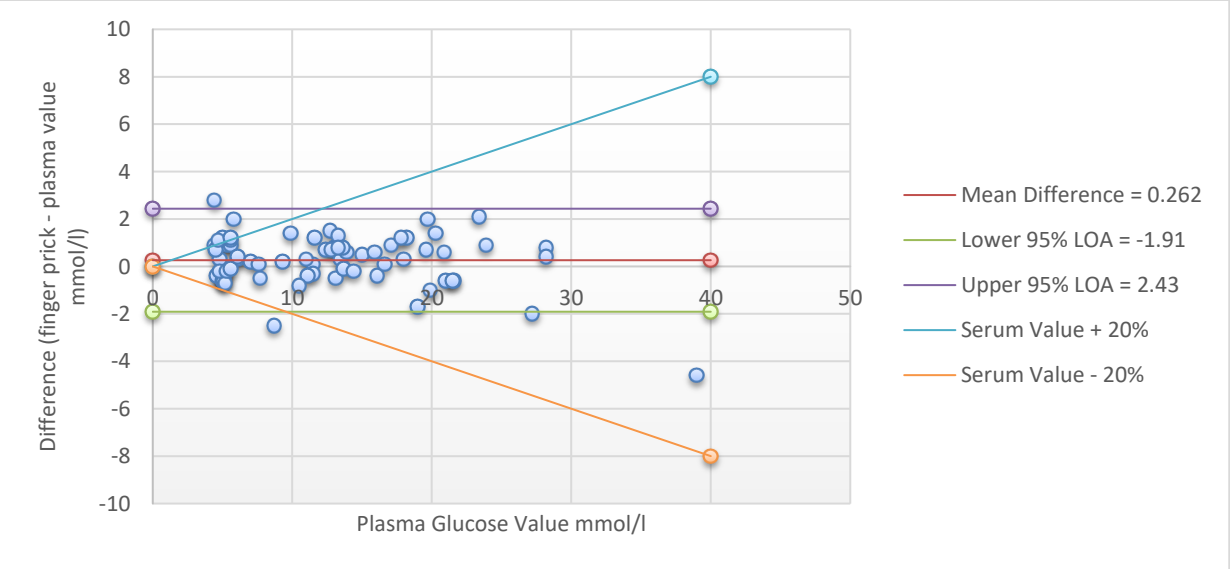


Figure 3. 4 Bland-Altman Plots for finger prick glucose BGA results compared to laboratory plasma glucose in healthy participants and acutely unwell diabetic patients combined.

The bland altman plot of the percentage differences for ear prick glucose compared with laboratory results are shown in Figures 3.5 – 3.7. The outlying result has been excluded because when included, the graphs were highly distorted as the y axis was extended to the extent where the other values were not easily distinguishable.

Figure 3.5. is the Bland Altman plot comparing the healthy participants' ear prick glucose results to the laboratory sample, using percent biases. The mean difference was 13.3%, as

opposed to zero (which would represent a comparable test) and the 95% limits of agreement were not within 20% of the plasma glucose values.

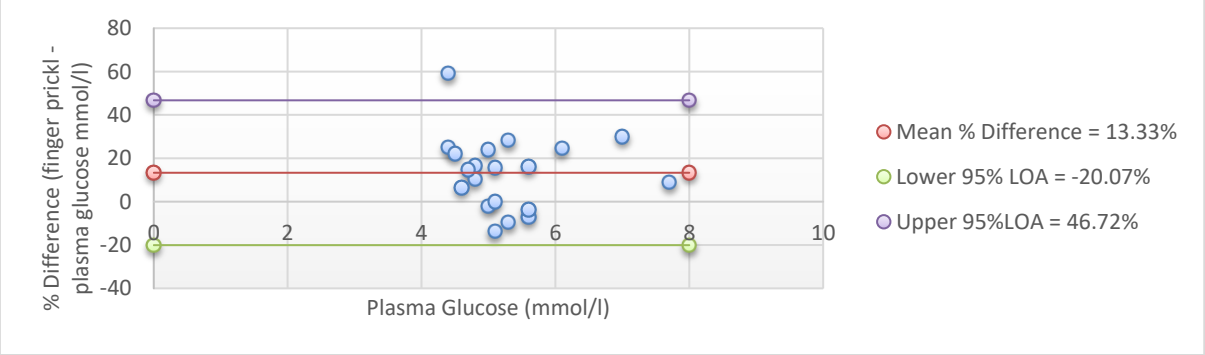


Figure 3. 5 Bland-Altman Plots for ear prick glucose BGA percentage bias compared to laboratory plasma glucose in healthy participants

Figure 3.6 compares the ear prick and laboratory glucose for the patient group. This demonstrates improved comparability with a mean difference closer to 0 and narrower limits of agreement, however, only the lower limit of agreement of 12.61% was within the required 20% of plasma values.

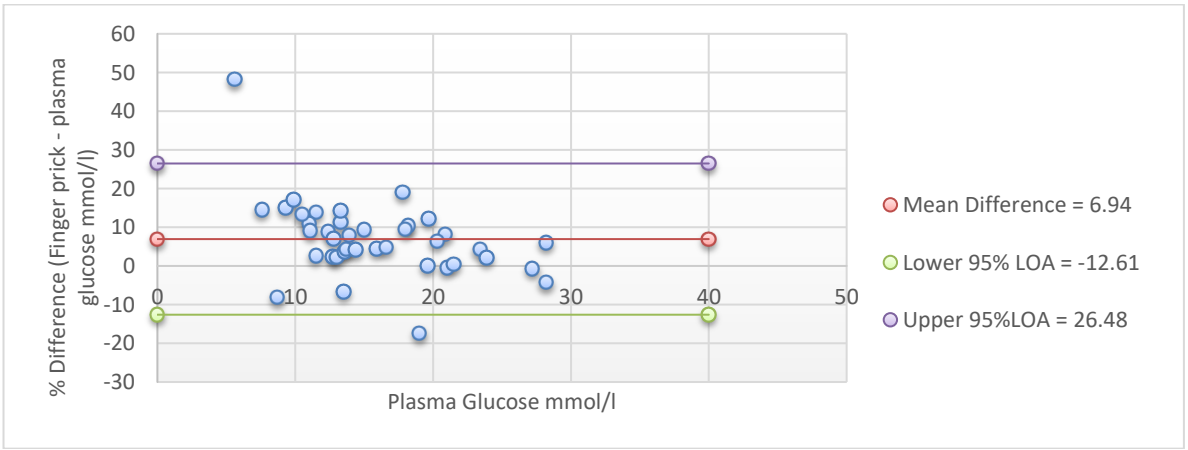


Figure 3. 6 Bland-Altman Plots for ear prick glucose BGA percentage bias compared to laboratory plasma glucose in acutely unwell diabetic patients

Figure 3.7 shows the combined results for all participants (healthy and diabetic). The LOA ranged from 16.4 to 34.63, and did not satisfy the ISO guidelines. There was also a substantial deviation from 0 for the mean percentage difference (9.1%).

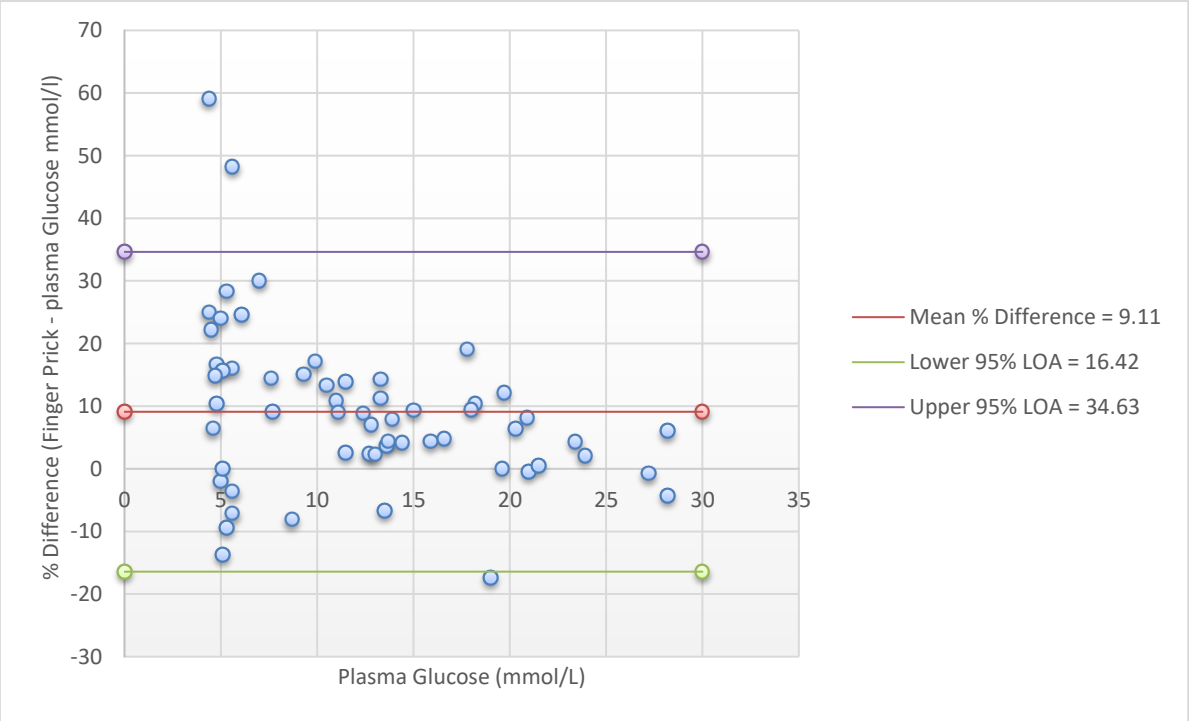


Figure 3. 7 Bland-Altman Plots for ear prick glucose BGA percentage bias compared to laboratory plasma glucose in healthy participants and acutely unwell diabetic patients combined.

Figure 3.8-3.9 show the Bland Altmann plots for the venous BGA glucose result compared to the laboratory sample result. This was normally distributed for both the ME and the percentage ME. Figure 3.8 shows the percentage differences (MEs) in healthy participants comparing venous BGA glucose to the laboratory sample. In this predominantly normoglycaemic range the LOA still failed to fall within the ISO guidelines of 20% (being 22.3% and 33.0%) and the mean percentage difference was still relatively high at 5%.

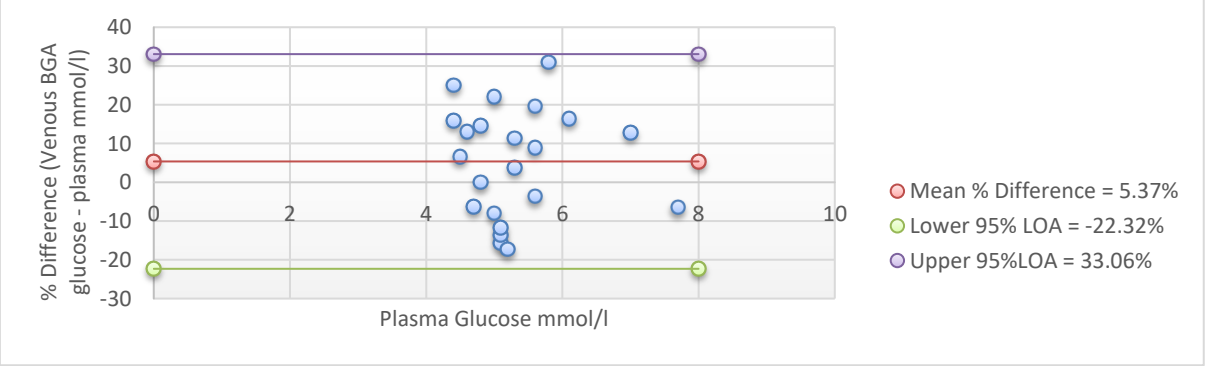


Figure 3. 8 Bland-Altman Plots for Venous glucose BGA percentage bias compared to laboratory plasma glucose in Healthy participants

Figure 3.9 compares the venous BGA glucose with the laboratory sample in the patient group. There is good concordance in values with the LOA within the ISO guideline of 20% and a mean difference of 2% in these samples.

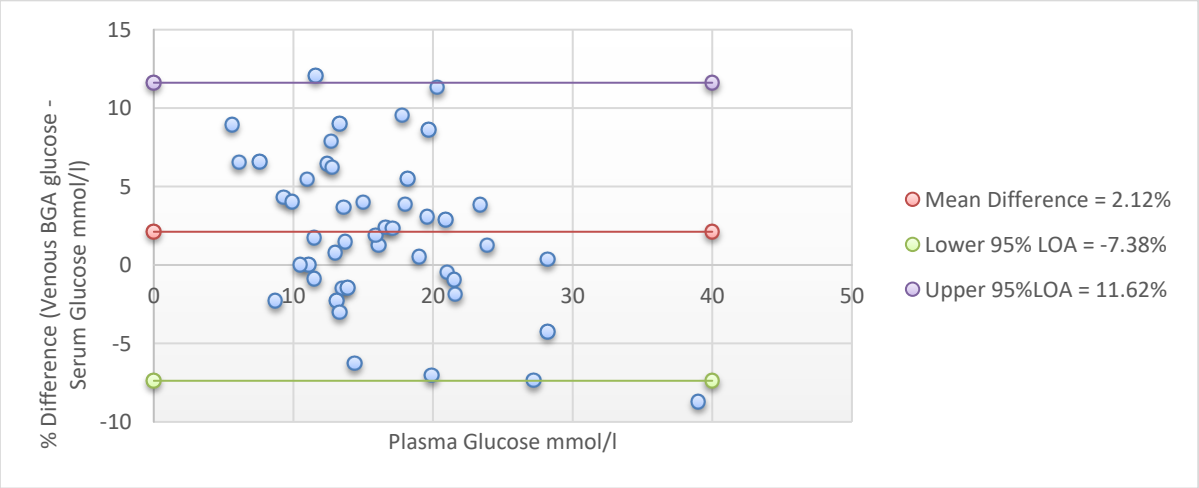


Figure 3. 9 Bland-Altman Plots for Venous glucose BGA percentage bias compared to laboratory plasma glucose in acutely unwell diabetic patients

Figure 3.10 compares venous BGA with laboratory samples for both patients and healthy participants, combined. The LOA fall just outside the set limits of 20% with an upper LOA of 20.7%. The figure also demonstrates that there was more discordance in normoglycaemic compared with hyperglycaemic values.

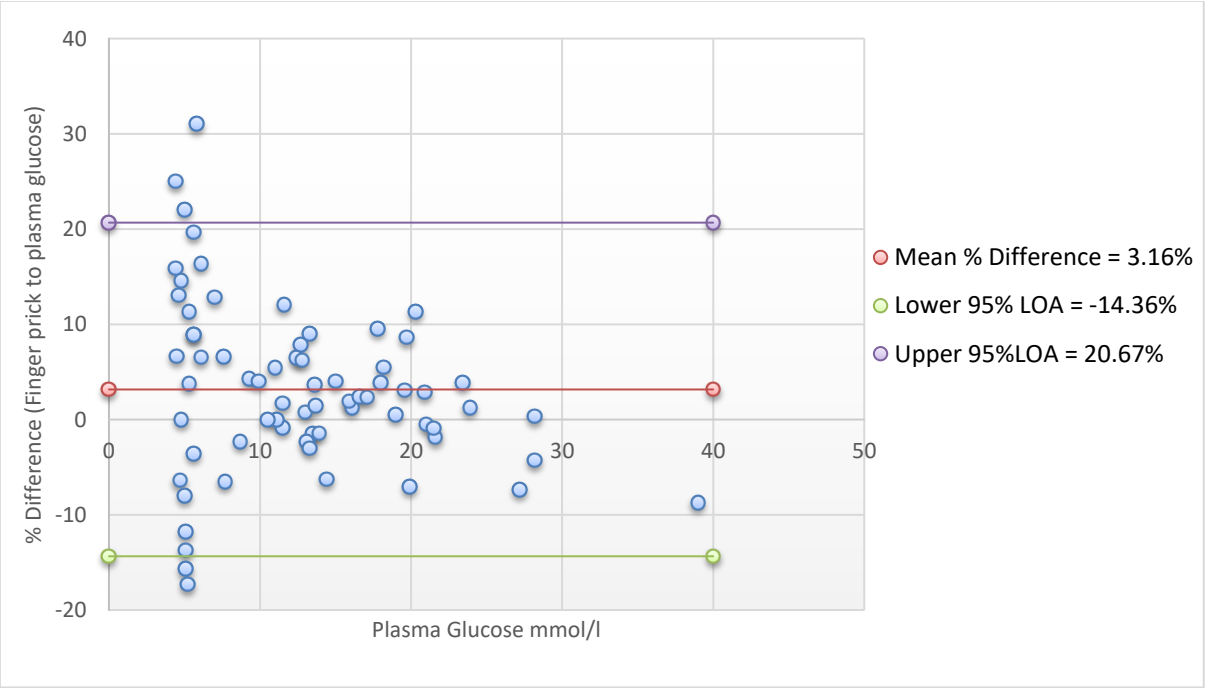


Figure 3. 10 Bland-Altman Plots for Venous glucose BGA percentage bias compared to laboratory plasma glucose in Healthy participants and acutely unwell diabetic patients combined.

Results compared to acceptability criteria

The acceptability criteria for glucose was derived from the IOC guidelines and state 95% of results should fall within 20% of a plasma sample. Under the assumptions used to calculate the 95% limits of agreement, the proportion lying within these guidelines have been calculated. Table 3.8 below shows these results. It shows that the criteria were met in the patient group finger prick samples and both patient and combined groups for the venous BGA results reflecting the results seen above.

	FP %	EP %	VP %
Healthy	67.2	62.7	81.3
Patient	98.8	69.4	100
Combined	87.4	68.1	96.5

Table 3. 8 The estimated percentage of samples meeting the acceptability for glucose for Finger prick (FP), Ear prick (EP) and Venous BGA (VP) in healthy, patient and combined groups

Comparison between groups

Table 3.9 below shows the results of the Friedman's test when the MEs between each of the methods of testing were compared (Finger prick, ear prick and venous prick). This shows that there was a statistically significant difference in the MEs between the different methods of testing with Chi-squared value of 22.908 and $p < 0.001$.

Test Statistics	
N	60
Chi-Square	22.908
df	2
Asymp. Sig.	<0.001

Table 3. 9 Results of Friedman's test between finger prick, ear prick and venous BGA glucose bias results

Post Hock analysis is shown in table 3.10 below. This demonstrates that there was no significant difference between the MEs of the finger prick and venous prick testing methods, however, finger prick and venous prick both showed statistically reduced MEs when compared to ear prick testing with p values of 0.002 and <0.001.

	EP - FP	VP - FP	VP - EP
Adjusted Significance	<0.001	1.00	0.001

Table 3. 10 Post hock analysis of bias results between Finger prick (FP), ear prick (EP) and venous BGA (VP) biases.

The results of the F tests of the MEs are shown in table 3.11 and 3.12 and below. This has been used to assess the difference between the range and hence width of the limits of agreement with a wider LOA reflecting a less reliable test (i.e. the ability to get the same result twice). This shows there were no statistically significant difference between the variance of the MEs and hence the range (width) of the limits of agreement between the healthy and patient groups in either the finger prick or the venous BGA sampling methods (p values 0.198 and 0.266 respectively) but was a statistically significant difference in the ear prick group (p-value 0.000) reflecting less reliability in the healthy group. When the sampling methods were compared against each other there was no statistically significant difference in the range of LOAs between the finger prick and venous BGA glucose samples (p values 0.058) but there was between the finger prick and ear prick as well as between the ear prick and venous BGA (p values <0.001). SO the LOAs are significantly narrower in the finger prick and venous BGA group when compared to the ear prick.

	FP	EP	VP
Healthy to patient	0.198	<0.001	0.266

Table 3. 11 Results of F-tests of the MEs in glucose results between healthy and patient groups for Finger prick (FP), Ear prick (EP) and venous BGA (VP).

	F test Result
FP to EP	<0.001
FP to VP	0.058
EP to VP	<0.001

Table 3. 12. Results of F-tests of the MEs in glucose results between Finger prick (FP), Ear prick (EP) and venous BGA (VP).

Comparison of results by age

As there was a significant age difference between healthy participants and patient groups, MEs were studied by quintile groups. Mean bias was then compared between these groups and significant differences between the groups compared using a Kruskal-Wallis test. Table 3.13 below shows the age range in each quintile and the mean bias for each sampling modality for both the healthy group and the patient group. It can be observed from this that there is no clear pattern between increasing age and changes to mean bias.

	Healthy				Patient Group			
Quintile	Age Range of Quintile	Mean Bias			Age Range of quintile	Mean bias mmol/l		
		FP	EP	VP		FP	EP	VP
1st	24 - 25	1.13	1	0.83	19 - 53.8	-0.22	1	0.01
2nd	25 - 28.2	0.34	1.35	0.08	53.8 – 63	0.34	-1.7	0.1
3rd	28.2 - 35.4	-0.1	0.35	0.05	63 – 74	0.16	0.82	0.53
4th	35.4 - 42	4	0.1	0.65	74 – 82	0.29	1.19	0.07
5th	42 - 49	0.42	0.28	0.28	82 – 87	0.47	0.58	0.32

Table 3. 13. Comparison of mean bias of glucose results when divided into age quintile groups in healthy group and patient groups for finger prick (FP), ear prick (EP) and venous BGA (VP) testing methods.

Following a Kruskal Wallis test comparing the combined quintile results there were no significant differences between the quintiles for any of the finger prick, ear prick or venepuncture sampling method (p values 0.907, 0.871 and 0.843 respectively). This confirms that there is no significant difference between the MEs in the different age groups.

Summary

The venous BGA glucose in the hyperglycaemic range met the acceptability criteria as stated. Finger prick glucose also did when glucose values were above 12mmol/l. None of the samples were sufficiently accurate in the normoglycaemic range. On direct comparison of the 3 sampling methods there was no significant difference between the accuracy of finger prick and venous BGA glucose measurement. However, both testing modalities were significantly more accurate and reliable (with significantly narrower limits of agreement) than the ear prick sampling method. There was also no significant difference in the differences between the age groups studied.

3.4.2 Sodium

Tables 3.15 to 3.17 summarise the sodium BGA results for the capillary finger prick, ear prick and venous samples compared to the gold standard, venous laboratory result. Incomplete datasets were collected in 2 subjects due to insufficient volume collection in capillary samples despite multiple attempts and 2 samples were reported as not received by the laboratory staff.

Table 3.14 below shows the results of the normality testing, confirming an approximate normal distribution of the MEs for this parameter.

	Kolmogorov-Smirnov			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
FP Bias	0.071	67	.200	0.979	67	0.305
EP Bias	0.102	61	0.183	0.953	61	0.02
VP Bias	0.103	69	0.067	0.986	69	0.624

Table 3. 14 Normality testing of the MEs for Finger Prick (FP), Ear Prick (EP) and Venous (VP) BGA sodium

Table 3.15 describes the finger prick BGA result compared to the venous serum sodium. The range of results (from 121.6 to 147.3) demonstrates the inclusion of parameters outside of the normal range. The healthy participants and the diabetic groups showed similar mean bias of 1.53 and 1.3mmol/l and limits of agreement of -1.15 to 4.63mmol/l and -1.9 to 4.5mmol/l respectively.

Participant group	Complete data set	Range of measurement Mmol/l	Mean bias mmol/l	Standard Deviation of the bias (mmol/l)	Lower 95% LOA bias	Upper 95% LOA bias
Healthy Participants	19/23	137.7 – 143.8	1.53	1.58	-1.57	4.63
Diabetic patients	48/48	121.6-147.3	1.3	1.63	-1.9	4.50
Combined	67/71	121.6-147.3	1.37	1.61	-1.79	4.52

Table 3. 15 Results of finger prick sodium compared to venous laboratory plasma samples in healthy participant group, patient group and combined results.

Ear prick results were compared to the laboratory samples (as described in table 3.16). Healthy participants had highly comparable results with a mean bias of 0.33mmol/l and 95% limits of agreement of -2.65 to 3.30. The diabetic group demonstrated less comparability with a mean bias more positive at 1.15mmol/l and 95% LOA further from the plasma samples at of -2.36 to 4.64.

Participant group	Complete data set	Range of measurement Mmol/l	Mean bias mmol/l	Standard Deviation of the bias (mmol/l)	Lower 95% LOA bias	Upper 95% LOA bias
Healthy Participants	20/23	134.8 – 143.5	0.33	1.52	-2.65	3.30
Diabetic patients	45/48	122.6 - 143	1.15	1.79	-2.36	4.64
Combined	65/71	122.6 - 143	0.88	1.73	-2.52	4.27

Table 3. 16 Results of Ear prick sodium compared to venous laboratory plasma samples in healthy participant group, patient group and combined results.

Sodium venous BGA results were compared to laboratory results (described in table 3.17) These show adequate comparability which was not dissimilar to the finger prick and ear prick results.

Participant group	Complete data set	Range of measurement Mmol/l	Mean bias mmol/l	Standard Deviation of the bias (mmol/l)	Lower 95% LOA bias	Upper 95% LOA bias
Healthy Participants	21/23	136.9 – 143.6	1.10	1.29	-1.43	3.63
Diabetic patients	48/48	121.4-144.7	0.85	1.52	-2.14	3.83
Combined	69/71	121.4 – 144.7	0.92	1.42	-1.92	3.77

Table 3. 17 Results of Venous BGA sodium compared to venous laboratory plasma samples in healthy participant group, patient group and combined results.

Figure 3.11 shows the Bland-Altman plot for the healthy participant finger prick sodium result compared to the venous serum gold standard. All of the sample results are within the US CLIA 4mmol/l guidelines but the 95% LOA exceed this, at -1.15 to 4.63 mmol/l with a mean difference of 1.53.

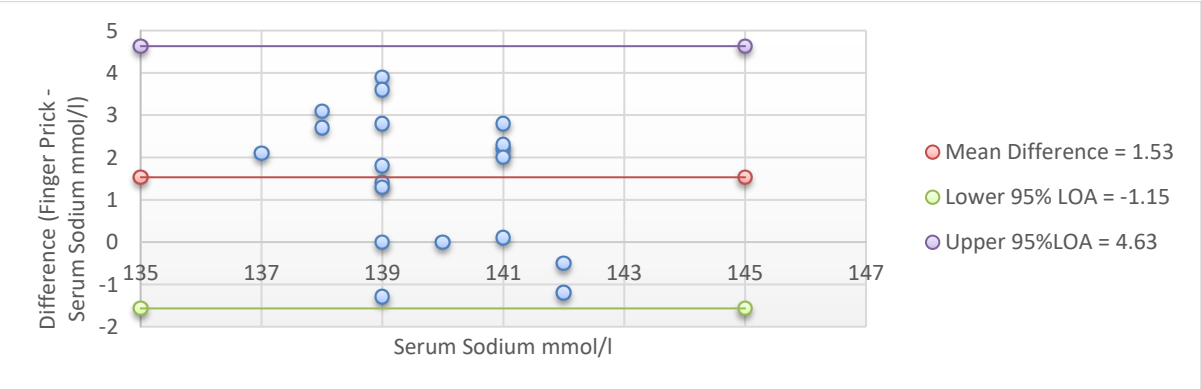


Figure 3. 11 Bland-Altman Plots for finger prick BGA sodium compared to laboratory serum sodium in Healthy participants

Figure 3.12 shows the Bland-Altman plot for the patients' finger prick sodium result compared to the venous serum gold standard. The 95% LOAs exceed the US CLIA recommendations, however, only one value lies outside this range with a 4.3mmol/l difference.

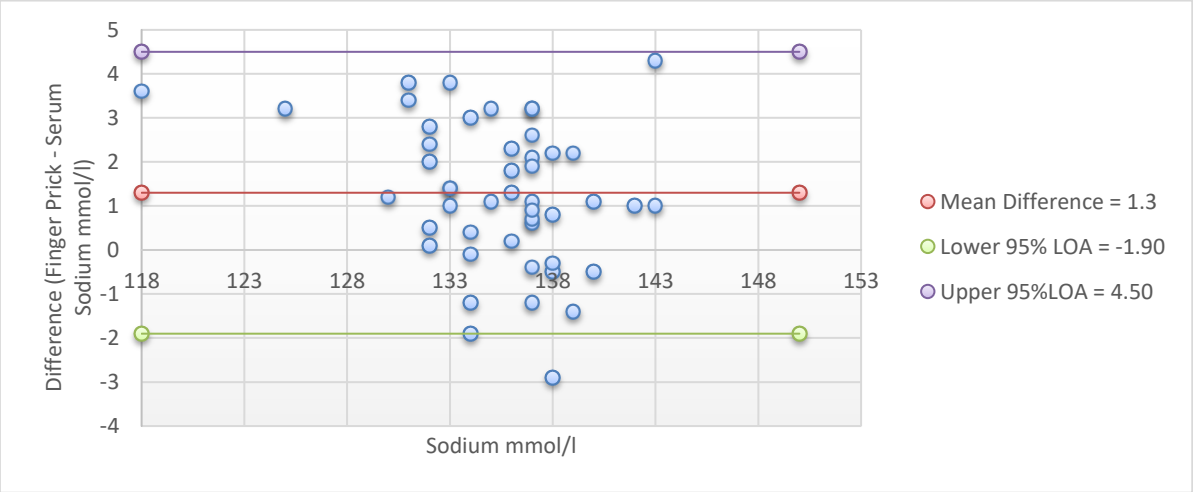


Figure 3. 12 Bland-Altman Plot for finger prick BGA sodium compared to laboratory serum sodium in acutely unwell diabetic patients

Figure 3.13 shows the Bland-Altman plot for healthy participants and patients' finger prick sodium result compared to the venous serum gold standard. When the datasets are combined, the upper limit of agreement does not lie within the 4mmol/l cut off.

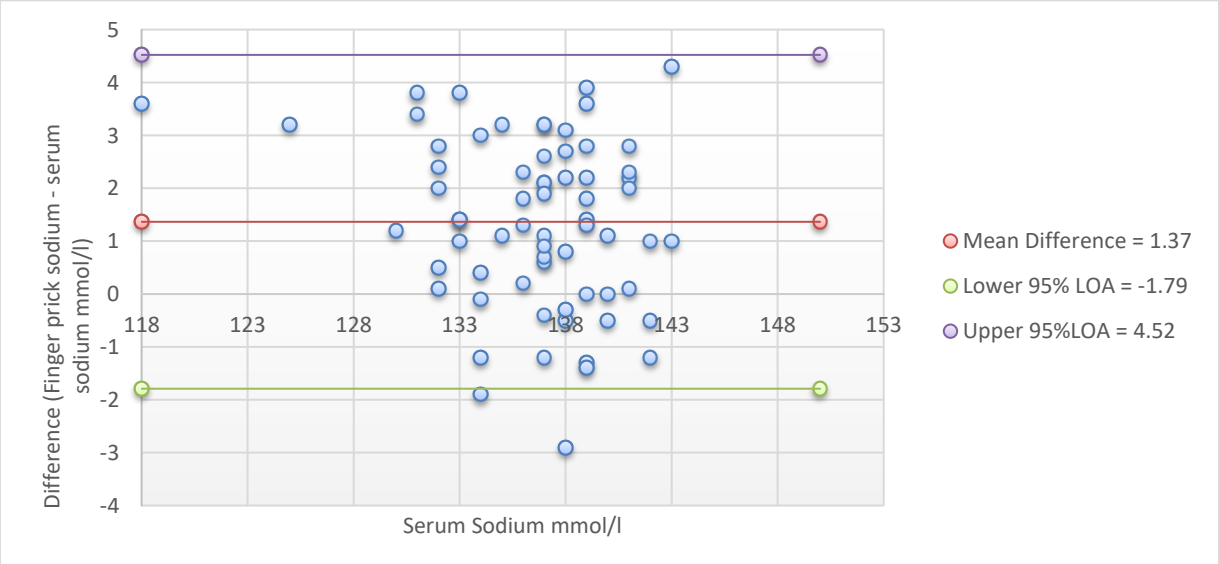


Figure 3. 13 Bland-Altman Plots for finger prick BGA sodium compared to laboratory serum sodium in healthy participants and acutely unwell diabetic patients combined.

Figure 3.14 compares the ear prick BGA sodium samples to the laboratory result in healthy participants. This shows a mean difference very close to 0 and relatively narrow 95% limits of agreement within the US CLIA guidelines.

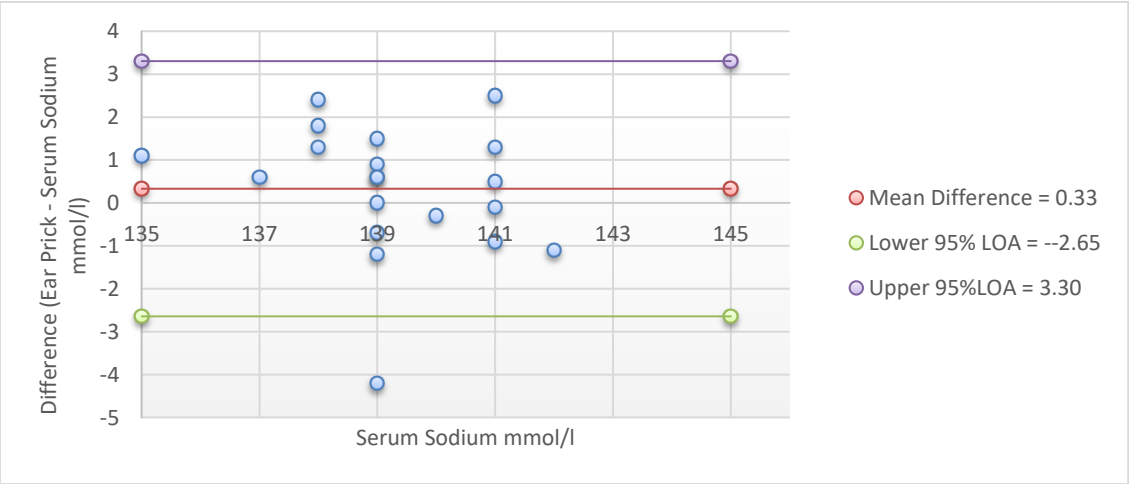


Figure 3. 14 Bland-Altman Plot for ear prick BGA sodium compared to laboratory serum sodium in Healthy participants

Figure 3.15 compares ear prick BGA sodium to laboratory values in patients. The 95% LOA do not meet the US CLIA guidelines as there were 2 samples outside 4mmol/l with one result showing 6mmol/l difference from the serum sodium sample.

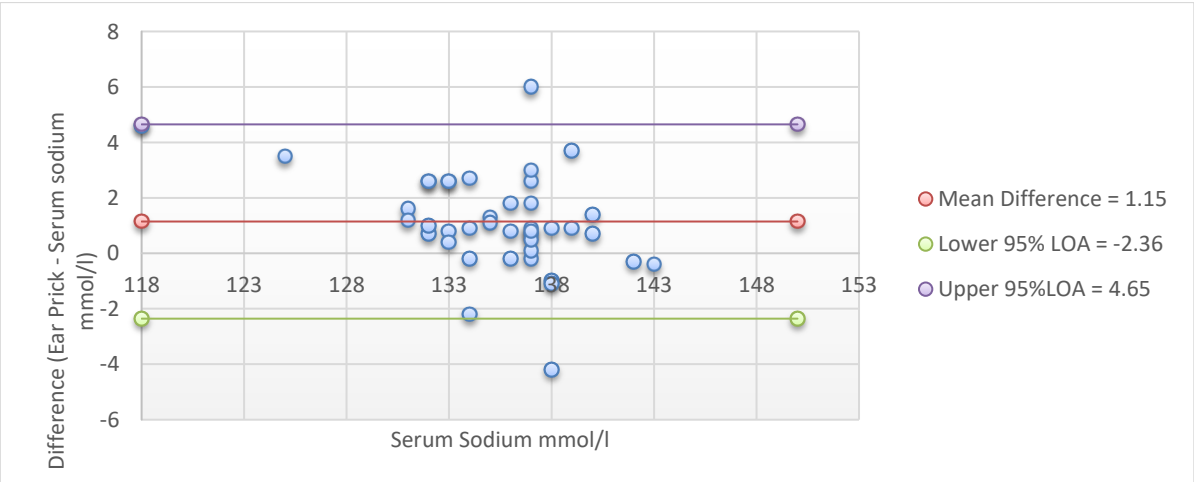


Figure 3. 15 Bland-Altman Plot for ear prick BGA sodium compared to laboratory serum sodium in acutely unwell diabetic patients

Figure 3.16 shows the combined patient and healthy participant results, comparing ear prick BGA to laboratory values. This demonstrated a positive mean difference and fairly narrow 95% limits of agreement but with an upper LOA higher than the 4mmol US CLIA set criteria.

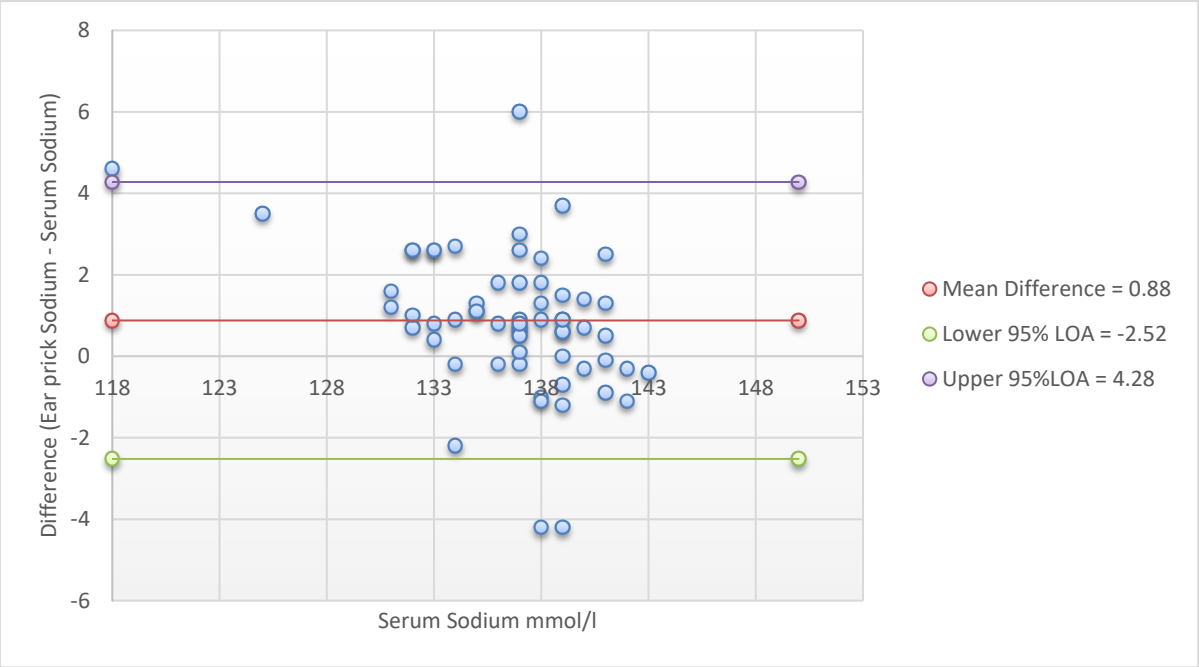


Figure 3. 16 Bland-Altman Plot for ear prick BGA sodium compared to laboratory serum sodium in Healthy participants and acutely unwell diabetic patients combined (Figure 3.12).

Figure 3.17 is the Bland-Altman plot for the healthy participant's venous BGA sodium compared to the serum values. All values were within the US CLIA 4 mmol/l guidelines, as were the 95% LOAs.

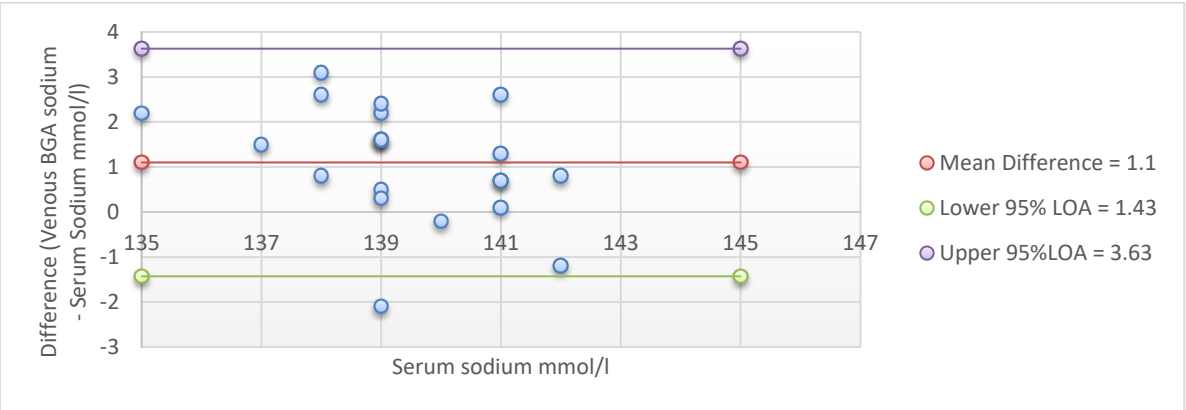


Figure 3. 17 Bland-Altman Plot for Venous BGA sodium compared to laboratory serum sodium in Healthy participants

Figure 3.18 compares venous BGA to laboratory sodium value in patients. The LOA were sufficiently narrow compared to the US CLIA guidelines with only one sample lying outside these 4mmol/l cut off.

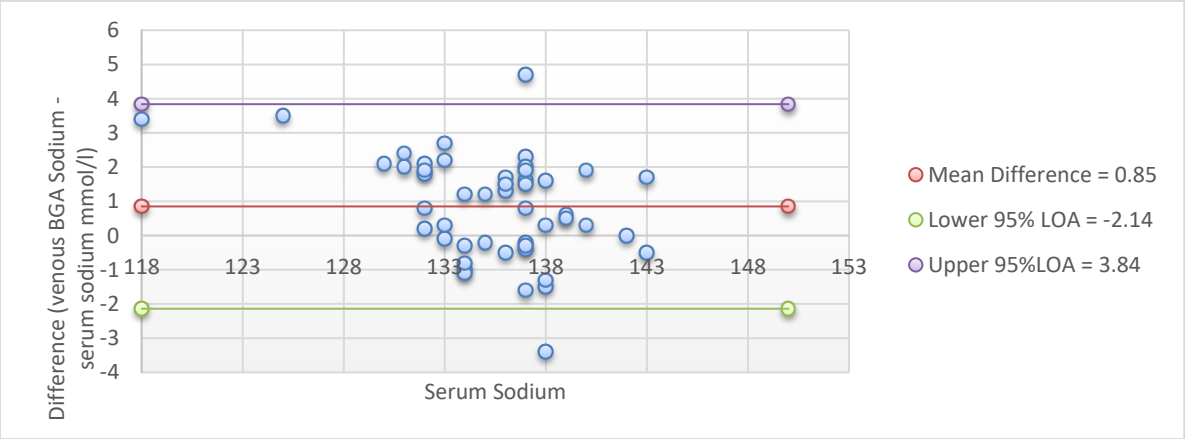


Figure 3. 18 Bland-Altman Plots for Venous BGA sodium compared to laboratory serum sodium in acutely unwell diabetic patients

Figure 3.19 compares venous BGA and laboratory sodium in both healthy participants and patients. The LOA fell within the required 4mmol/l with a difference of less than 1 mmol/l for the mean bias.

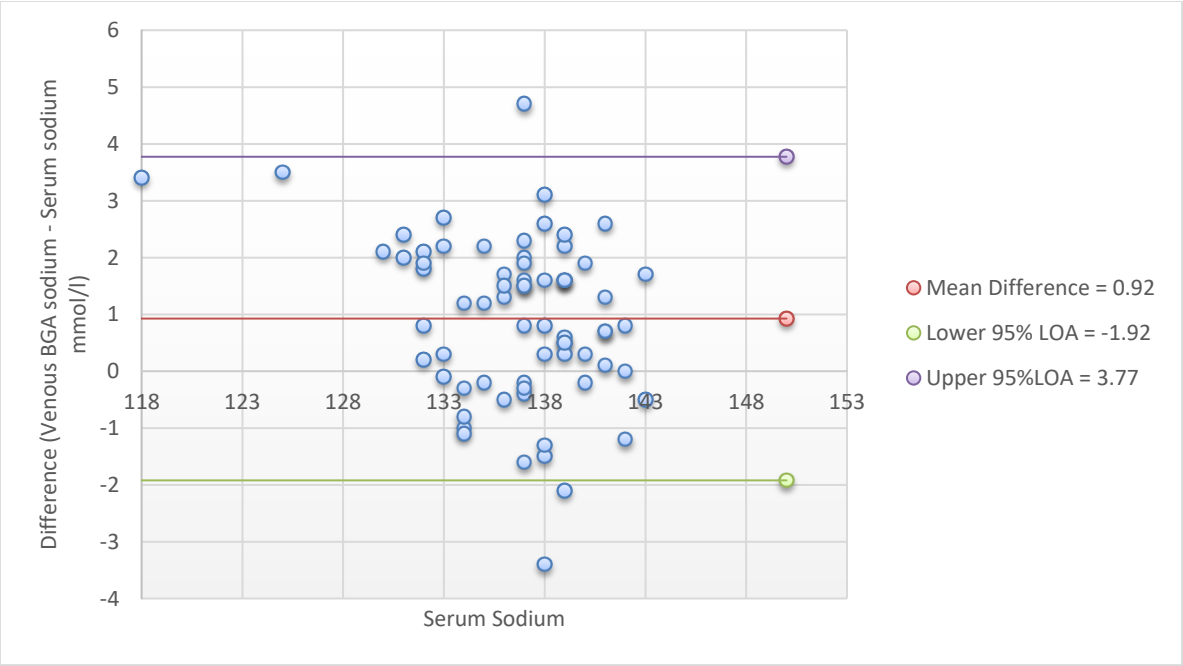


Figure 3. 19 Bland-Altman Plots for Venous BGA sodium compared to laboratory serum sodium in healthy participants and acutely unwell diabetic patients combined

Results compared to acceptability criteria

The acceptability criteria for sodium was derived from the US CLIA guidelines and state 95% of results should fall within 4mmol/ of a serum sample. Table 3.18 below shows the percentage of samples that fulfil these criteria for each sampling method based on the assumptions made for the calculations of the limits of agreement. It shows that there was only the finger prick healthy and combined groups and the ear prick patient group that marginally failed to meet this criterion by less than 1%.

	FP %	EP %	VP %
Healthy	94.1	99.0	98.8
Patient	95.0	94.3	98.0
Combined	94.8	96.5	98.2

Table 3. 18 The estimated percentage of samples meeting the acceptability for sodium for Finger prick (FP), Ear prick (EP) and Venous BGA (VP) in healthy, patient and combined groups

Comparison between groups

Table 3.19 below shows the results of the Friedman's test when the MEs between each of the methods of testing were compared (Finger prick, ear prick and venous prick). This shows that there were significant differences of the MEs between these groups with chi-squared value of 11 and p value of 0.003

Test Statistics	
N	59
Chi-Square	11.489
df	2
Asymp. Sig.	.003

Table 3. 19 Results of Friedman's test between finger prick, ear prick and venous BGA sodium ME results

Post Hock analysis is shown in table 3.20, below. There were statistically significant difference between the MEs of the finger prick and both the other sampling methods (p values 0.015 and 0.008), with the highest level of ME for the finger prick sampling method. There were no statistically significant differences between the venous BGA ME and the ear prick (p-value 1.00).

	EP - FP	VP - FP	VP - EP
Adjusted Significance	0.015	0.008	1.00

Table 3. 20 Post hoc analysis of ME results between Finger prick (FP), ear prick (EP) and venous BGA (VP) biases using.

The results of the F tests of the biases for sodium are shown in table 3.21 and 3.22, below. There were no statistically significant differences in the width of the LOAs between the healthy and patient groups in any of the testing methods but also not between each of the testing methods with no p values less than 0.05.

	FP	EP	VP
Healthy to patient	0.916	0.448	0.419

Table 3. 21 Results of F-tests of the ME in sodium results between healthy and patient groups for Finger prick (FP), Ear prick (EP) and venous BGA (VP).

	F test Result
FP to EP	0.555
FP to VP	0.401
EP to VP	0.157

Table 3. 22. Results of F-tests of the ME in sodium results between Finger prick (FP), Ear prick (EP) and venous BGA (VP).

Comparison of results by age

The age difference between healthy and patient groups was studied by quintile groups. Table 3.23 below shows the age range in each quintile and the mean bias for each sampling modality for both the healthy and the patient group. It can be observed that there was no clear pattern between increasing age and changes to mean bias.

	Healthy				Patient Group			
Quintile	Age Range of Quintile	Mean Bias			Age Range of Quintile	Mean bias mmol/l		
		FP	EP	VP		FP	EP	VP
1st	24 - 25	2.73	0.5	1.53	19 - 53.8	2.69	2.82	2.23
2nd	25 - 28.2	1.28	1	0.96	53.8 - 63	0.53	0.24	0.37
3rd	28.2 - 35.4	0	0.25	1.73	63 - 74	0.95	0.78	0.66
4th	35.4 - 42	0.23	2.55	1.33	74 - 82	1.18	0.36	0.57
5th	42 - 49	0.4	-1.43	-0.48	82 - 87	1.29	1.16	0.52

Table 3. 23 Comparison of mean bias for sodium when divided into age quintile groups in healthy group and patient group for finger prick (FP), ear prick (EP) and venous BGA (VP) testing methods

Following a Kruskal Wallis test comparing the combined quintile results there were no significant differences between the quintiles for the finger prick, ear prick or venepuncture sampling method (p values 0.34, 0.599 and 0.325 respectively). This confirmed that there was no significant difference between the MEs in the different age groups.

Summary

All venous BGA sodium results met the acceptability criteria and had 95% limits of agreement within the 4mmol/l guidelines (FederalRegister 1992). The ear prick samples also met acceptability criteria for healthy controls and combined groups but not patients. The finger prick test for both healthy and combined groups also failed to reach the required level of acceptability by less than 1% but did for the patient group. When comparing the three different sampling methods, there were no significant differences between the ear prick and venous BGA methods, however, finger prick was significantly less accurate than the other 2 sampling methods despite having 94.8% of the samples reaching guideline levels of concordance.

3.4.3 Potassium

Tables 3.25 to 3.27 summarise the results from the potassium BGA results for the capillary finger prick, ear prick and venous samples compared to the gold standard, venous laboratory result. The Bland-Altman plots for the corresponding data follows (figures 3.20-3.22).

Table 3.24 shows the results of normality testing, confirming an approximate normal distribution of the MEs for this parameter.

	Kolmogorov-Smirnov			Shapiro-Wilk		
	Statistic	Df	Sig.	Statistic	df	Sig.
FP Bias	0.092	69	.200*	0.968	69	0.076
EP Bias	0.103	61	0.178	0.971	61	0.158
VP Bias	0.125	69	0.009	0.914	69	0

Table 3. 24. Normality testing of the MEs for Finger Prick (FP), Ear Prick (EP) and Venous (VP) BGA potassium

Table 3.25 describes the finger prick BGA potassium compared to the venous serum result. The range of results (3.34 to 5.41mmol/l) did not deviate far from physiologically normal values. The patient mean bias (0.15mmol/l), was closer to the serum value compared to the healthy participants (mean bias of -2.86). However the 95% LOA in the healthy group (-0.656 to 0.083mmol/l) were narrower than that of the patient group (-0.686 to 0.386) but not significantly so (see f test results below).

Participant group	Complete data set	Range of measurement mmol/l	Mean bias mmol/l	Standard Deviation of the bias (mmol/l)	Lower 95% LOA bias	Upper 95% LOA bias
Healthy Participants	21/23	3.53-4.48	-0.286	0.188	-0.656	0.083
Diabetic patients	48/48	3.34-5.41	-0.15	0.273	-0.686	0.386
Combined	69/71	3.34-5.41	-0.191	0.257	-0.695	0.312

Table 3. 25 Results of finger prick potassium compared to venous laboratory plasma samples in healthy participant group, patient group and combined results.

Table 3.26 describes the ear prick data for potassium. The patient group for this method of blood collection was the only one of all the sampling methods to show a positive mean bias of 0.048 mmol/l. The healthy group had mean bias of -0.131 with 95% LOAs of -0.66 and 0.398, significantly narrower than the relatively wide patient group (-0.77 to 0.867), (p=0.044, see f test below).

Participant group	Complete data set	Range of measurement mmol/l	Mean bias mmol/l	Standard Deviation of the bias (mmol/l)	Lower 95% LOA bias	Upper 95% LOA bias
Healthy Participants	20/23	3.6-4.97	-0.131	0.270	-0.66	0.398
Diabetic patients	41/48	3.57-5.82	0.048	0.418	-0.77	0.867
Combined	61/71	3.57-5.82	-0.011	0.383	-0.762	0.740

Table 3. 26 Results of Ear prick potassium compared to venous laboratory plasma samples in healthy participant group, patient group and combined results.

Table 3.27 describes venous BGA potassium. The mean bias for this method of blood sampling was further from 0 than the finger prick and ear prick groups (mean bias of -0.467 in the healthy participant groups, -0.362 for the diabetic group and -0.394 for the combined results). This led to an almost completely negative range of LOA, from -0.793 to 0.004 in the combined group.

Participant group	Complete data set	Range of measurement mmol/l	Mean bias mmol/l	Standard Deviation of the bias (mmol/l)	Lower 95% LOA bias	Upper 95% LOA bias
Healthy Participants	21/23	3.31-4.31	-0.467	0.116	-0.695	-0.239
Diabetic patients	48/48	3.29-5.48	-0.362	0.225	-0.804	0.079
Combined	69/71	3.29-5.48	-0.394	0.203	-0.793	0.004

Table 3. 27 Results of Venous BGA potassium compared to venous laboratory plasma samples in healthy participant group, patient group and combined results.

The Bland-Altman plot for the healthy participant's finger prick potassium compared to the laboratory serum venous sample is shown in Figure 3.20. The 95% LOA were not within the US CLIA 0.5mmol/l guidelines, with the lower limit LOA less than -0.66mmol/l due to a low mean difference of -0.29.

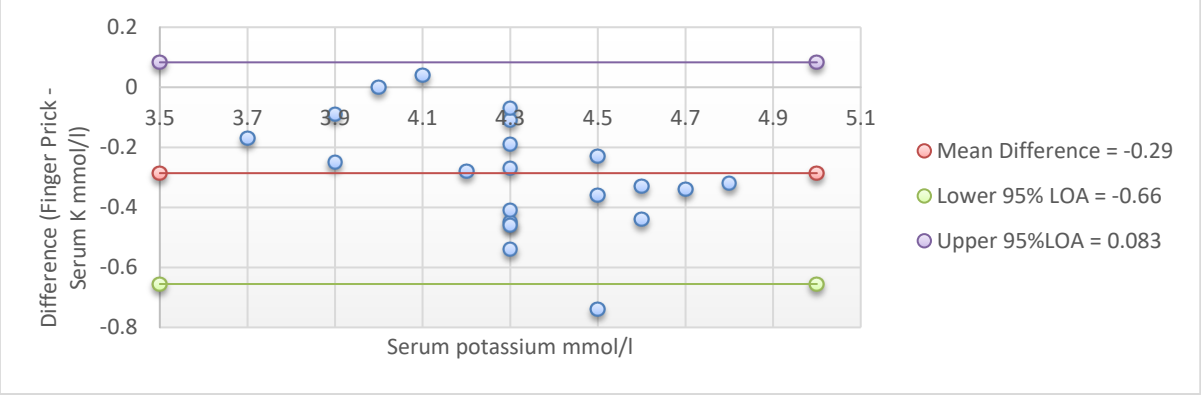


Figure 3. 20 Bland-Altman Plot for finger prick potassium results compared to laboratory serum potassium in healthy participants.

The Bland Altman plot comparing the patients' finger prick to laboratory potassium is shown in figure 3.21 below. The mean difference was negative and the lower LOA exceeded the US CLIA guidelines of 0.5mmol/l (FederalRegister 1992).

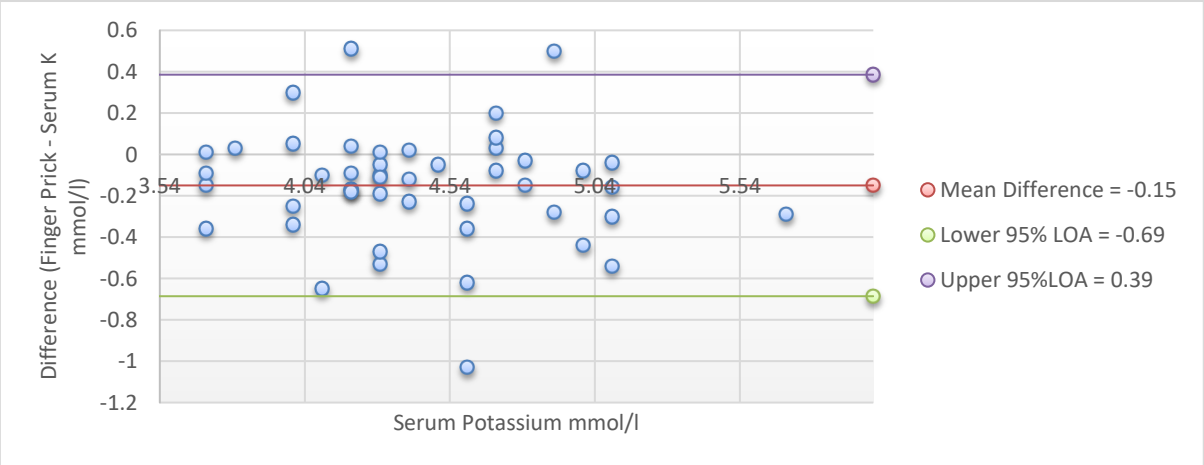


Figure 3. 21 Bland-Altman Plot for finger prick potassium results compared to laboratory serum potassium in acutely unwell diabetic patients.

The Bland Altman plot comparing finger prick to laboratory potassium for all participants is shown in figure 3.22. The lower limit of agreement did not satisfy the US CLIA criteria of 95% of results falling within 0.5mmol/l of the gold standard test. Both this and the previous figure (3.21) highlight the presence of an outlying sample which was 1.03mmol/l less than the serum potassium sample.

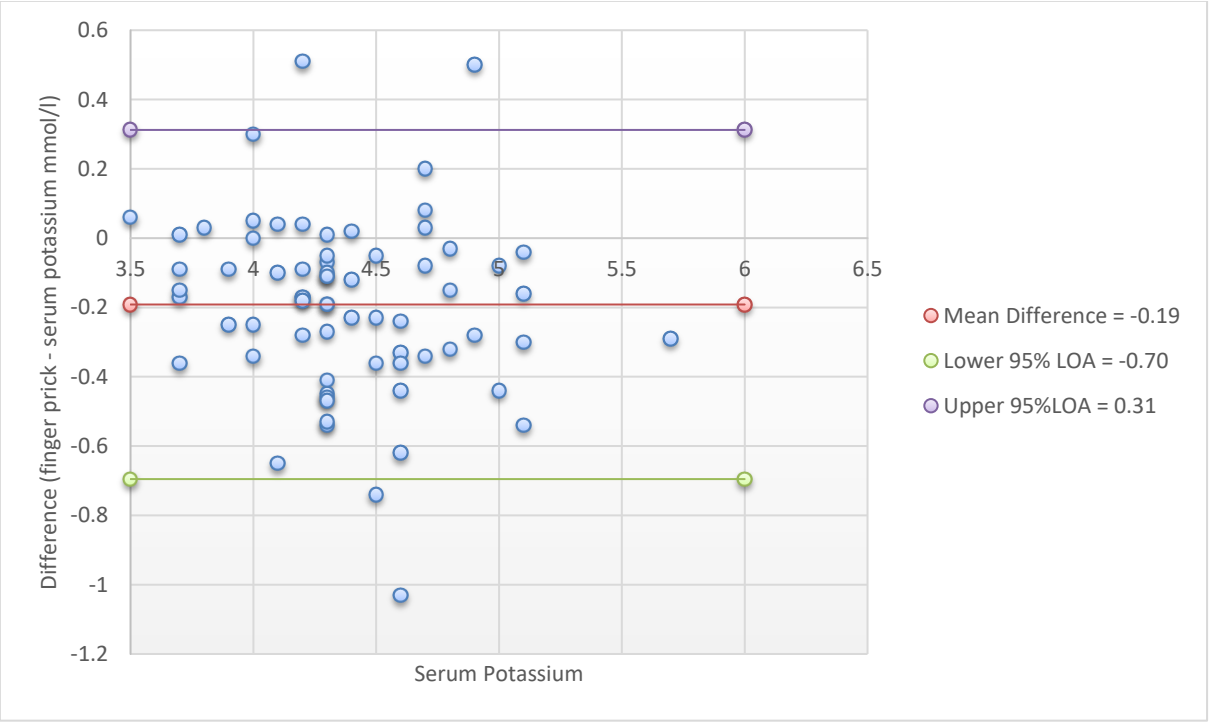


Figure 3. 22 Bland-Altman Plot for finger prick potassium results compared to laboratory serum potassium in healthy participants and acutely unwell diabetic patients combined.

Figure 3.23 shows the Bland Altman plot comparing ear prick BGA and laboratory potassium results in healthy participants. The mean difference was negative and the lower LOA exceeded the US CLIA guidelines.

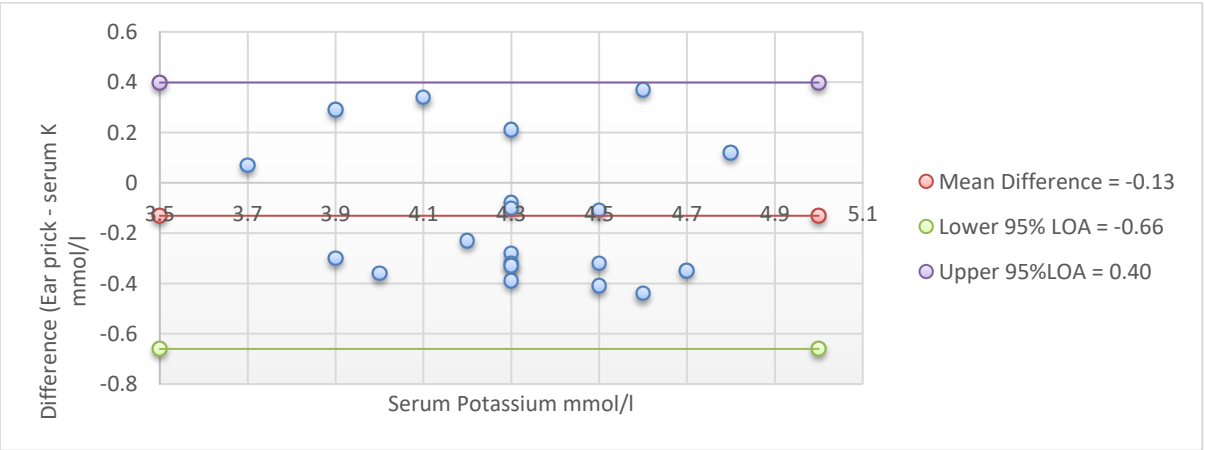


Figure 3. 23 Bland-Altman Plots for ear prick potassium results compared to laboratory serum potassium in healthy participants.

Figure 3.24 demonstrates the Bland Altman plot comparing ear prick and laboratory potassium in patients. The mean difference was close to zero but the 95% LOA exceed the US CLIA guidelines.

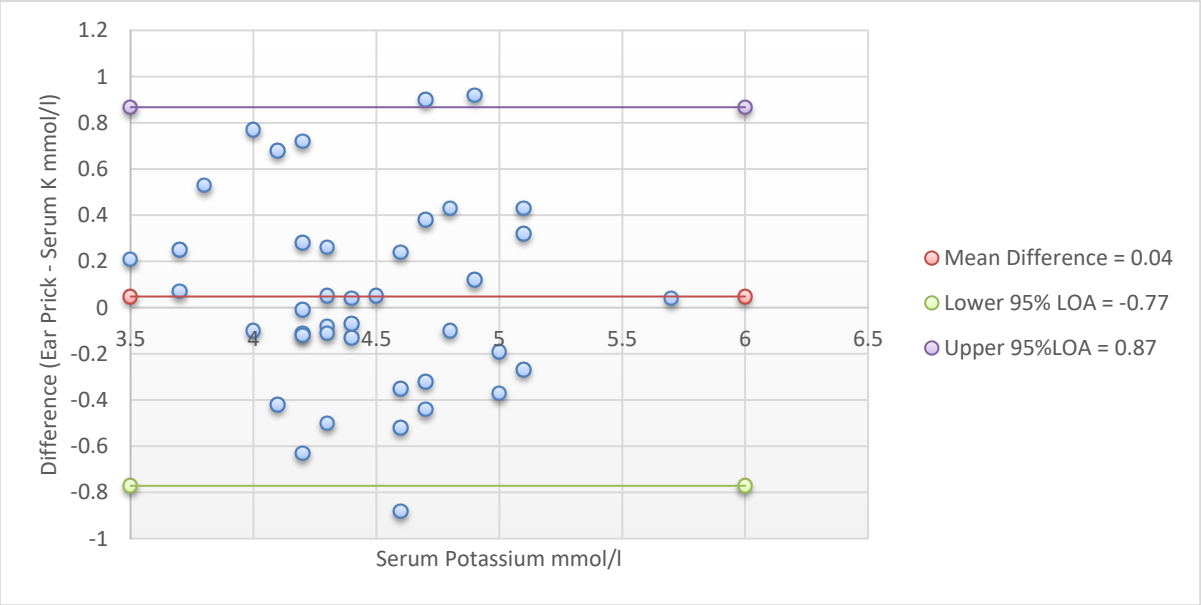


Figure 3. 24 Bland-Altman Plot for ear prick potassium results compared to laboratory serum potassium acutely unwell diabetic patients.

When results from healthy participants and patients were combined, neither the upper or lower 95% LOA satisfied the US CLIA criteria (see Figure 3.25). This figure also illustrates three data points which were >0.8 mmol/l from the serum values.

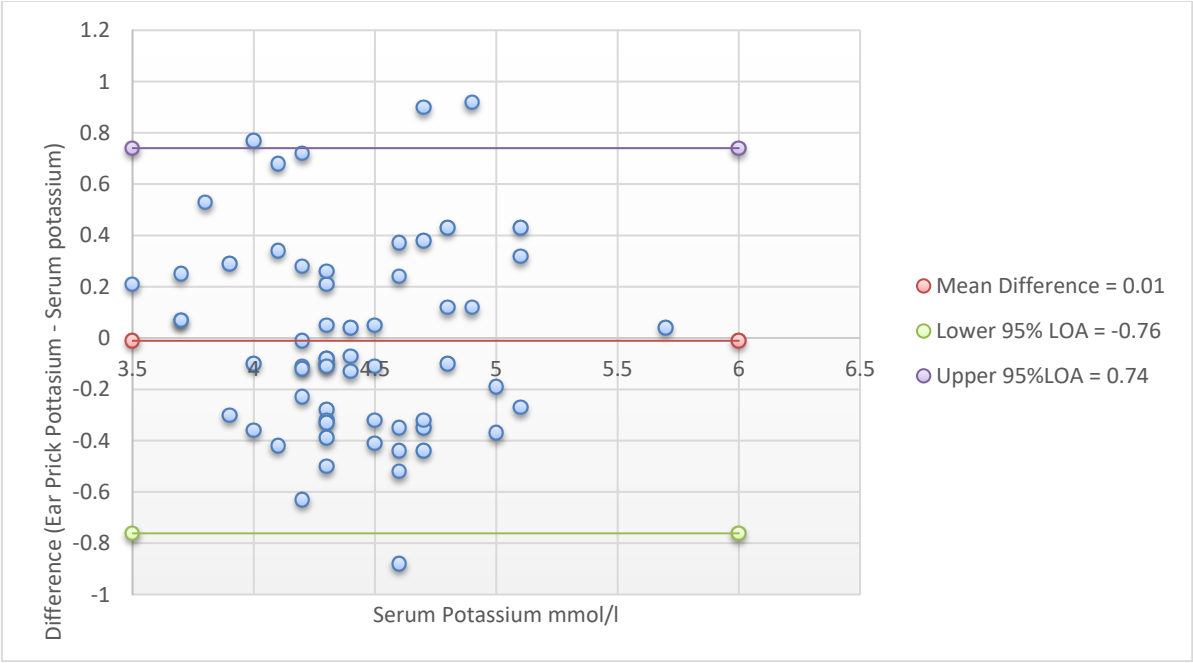


Figure 3. 25 Bland-Altman Plot for ear prick potassium results compared to laboratory serum potassium in healthy participants and acutely unwell diabetic patients combined

Finally, venous BGA potassium results were compared to the venous serum laboratory values in healthy controls (figure 3.26), patients (figure 3.27) and all participants (figure 3.28). In healthy participants, the BGA samples were consistently less than the serum laboratory samples, with a mean difference of almost -0.5mmol/l. The 95% limits of agreement were narrow, however, with a difference of only 0.46mmol/l.

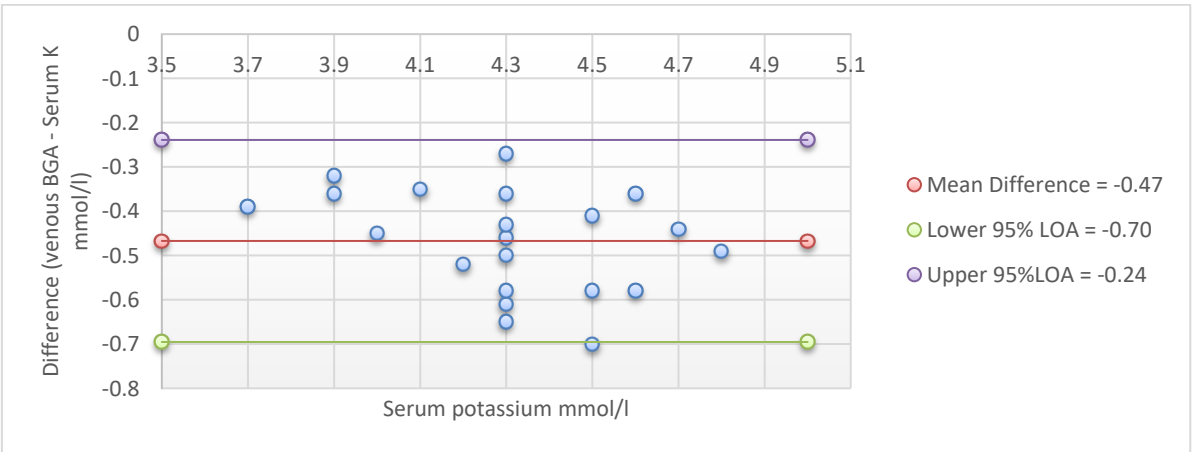


Figure 3. 26 Bland-Altman Plot for Venous BGA results compared to laboratory serum potassium in healthy participants.

Figure 3.27 shows the Bland Altman plot for patient venous BGA compared with the laboratory result. In this case the 95% LOA exceeded accepted criteria.

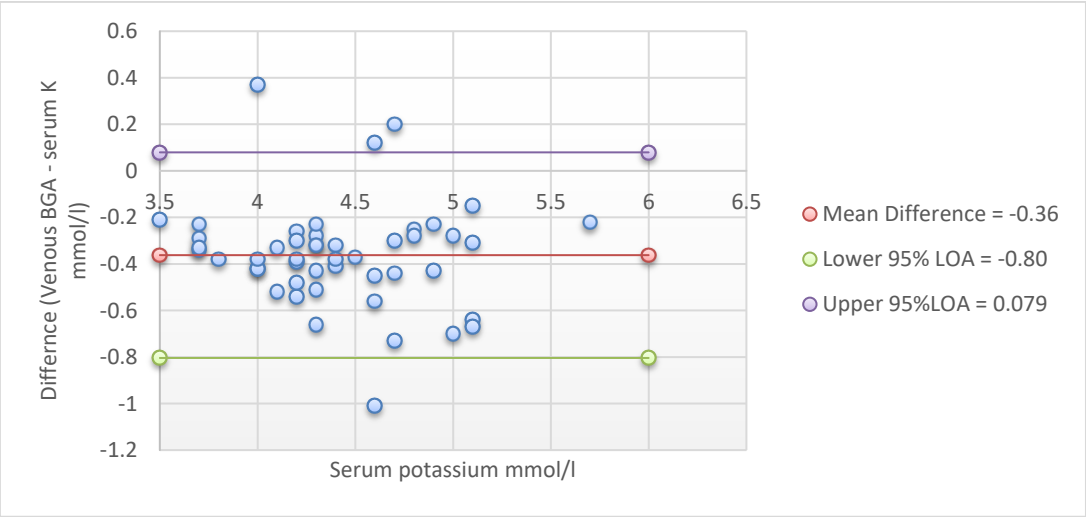


Figure 3. 27 Bland-Altman Plot for Venous BGA results compared to laboratory serum potassium in acutely unwell diabetic patients combined.

Figure 3.28 shows the Bland Altman plot for the combined healthy and patient venous BGA and laboratory result. Once again, a negative bias was seen and the LOA failed to meet the US CLIA guidelines.

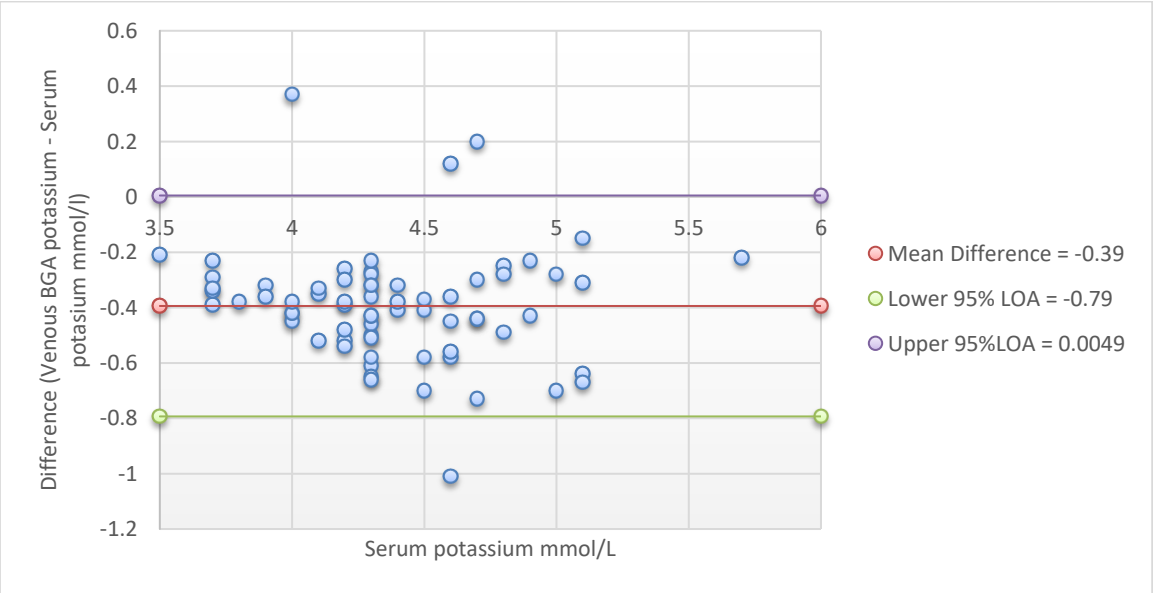


Figure 3. 28 Bland-Altman plots for Venous BGA results compared to laboratory serum potassium in healthy participants and acutely unwell diabetic patients combined.

Results compared to acceptability criteria

The acceptability criterion for potassium was derived from the US CLIA guidelines and state 95% of results should fall within 0.5mmol/ of a serum sample (FederalRegister 1992). Table 3.28 below shows the results for percentage of samples that fulfil these criteria based on the assumptions for calculation of LOAs for each sampling method. It shows that the criteria were not met in any of the sampling methods. The venous BGA samples had less than 70% fulfilling the criteria.

	FP %	EP %	VP %
Healthy	87.2	90.4	61.1
Patient	89.1	76.5	72.9
Combined	88.0	80.8	69.8

Table 3. 28 The estimated percentage of samples meeting the acceptability for potassium for Finger prick (FP), Ear prick (EP) and Venous BGA (VP) in healthy, patient and combined groups

Comparison between groups

Table 3.29 below shows the results of the Friedman's test when the MEs between each of the methods of testing are compared (Finger prick, ear prick and venous prick). This shows that there were significant differences between the biases between these groups with chi-squared value of 60.5 and p value of <0.001.

Test Statistics	
N	61
Chi-Square	60.570
df	2
Asymp. Sig.	<0.001

Table 3. 29 Results of Friedman's test between finger prick, ear prick and venous BGA potassium bias results

Post Hoc analysis is shown in table 3.30, below. This shows that there were statistically significant differences between all of the sampling methods with ear prick testing showing reduced levels of ME compared to both of the other sampling methods. Furthermore, finger prick samples had reduced levels of ME compared to venous BGA bias (p values all <0.001).

	EP - FP	VP - FP	VP - EP
Adjusted Significance	0.01	<0.001	<0.001

Table 3. 30 Post hoc analysis of ME results between Finger prick (FP), ear prick (EP) and venous BGA (VP) using Wilcoxan signed ranks test.

The results of the F tests of the MEs for potassium are shown in table 3.31 and 3.32, below. There were statistically significant differences between the range of the LOAs between the healthy and patient groups in the ear prick and venous BGA groups but not in the finger prick group. When the sampling methods were compared there were also statistically significant differences between the range of LOAs in the finger prick to ear prick and ear prick to venous prick, confirming that wide LOAs seen in the ear prick group are significantly wider than the other 2 sampling methods.

	FP	EP	VP
Healthy to patient	0.072	0.044	0.002

Table 3. 31 Results of F-tests of the MEs in potassium results between healthy and patient groups for Finger prick (FP), Ear prick (EP) and venous BGA (VP).

	F test Result
FP to EP	0.002
FP to VP	0.057
EP to VP	<0.001

Table 3. 32. Results of F-tests of the biases in potassium results between Finger prick (FP), Ear prick (EP) and venous BGA (VP).

Comparison of results by age

Parameters measurement error was studied by age quintile groups. Table 3.33 below shows the age range in each quintile and the mean bias for each sampling modality for both the healthy group and the patient group. There was no clear pattern between increasing age and changes to mean bias. However, there was a generally higher bias in the youngest quintile group.

	Healthy				Patient Group			
Quintile	Age Range of Quintile	Mean Bias			Age Range of quintile	Mean bias mmol/l		
		FP	EP	VP		FP	EP	VP
1st	24 - 25	2.73	0.5	1.53	19 - 53.8	2.69	2.82	2.23
2nd	25 - 28.2	1.28	1	0.96	53.8 - 63	0.53	0.24	0.37
3rd	28.2 - 35.4	0	0.25	1.73	63 - 74	0.95	0.78	0.66
4th	35.4 - 42	0.23	2.55	1.33	74 - 82	1.18	0.36	0.57
5th	42 - 49	0.4	-1.43	-0.48	82 - 87	1.29	1.16	0.52

Table 3. 33 Comparison of mean bias for potassium when divided into age quintile groups in healthy group and patient group for finger prick (FP), ear prick (EP) and venous BGA (VP) testing methods

Following a Kruskal-Wallis test comparing the combined quintile results there were no significant differences between the quintiles for the ear prick or venepuncture sampling methods (p values 0.106, 0.061 respectively). There was, however, statistical difference between the quintile groups in the finger prick method, p = 0.008.

Summary

The BGA finger prick, ear prick and venous potassium results were insufficiently accurate to fulfil the US CLIA guidelines and gave results consistently lower than the gold standard laboratory samples. When comparing the different methods of testing, ear prick was the

most accurate followed by finger prick and then the venous BGA method, however the ear prick has significantly wider limits of agreement than either the finger prick or the venous BGA test suggesting a less reliable test (i.e. the ability to produce reproduce the same results).

3.4.4 Haemoglobin

Tables 3.35 to 3.37 summarise the haemoglobin BGA results for the capillary finger prick, ear prick and venous samples compared to the gold standard, venous laboratory result..

The Bland-Altman plots for the corresponding data follows (figures 3.29-3.37). Table 3.34 describes normality testing. This confirms an approximate normal distribution of the MEs for this parameter.

	Kolmogorov-Smirnov			Shapiro-Wilk		
	Statistic	Df	Sig.	Statistic	df	Sig.
FP Bias	0.066	69	.200*	0.988	69	0.772
EP Bias	0.09	60	.200*	0.975	60	0.268
VP Bias	0.086	70	.200*	0.951	70	0.009

Table 3. 34 Normality testing of theMEss for Finger Prick (FP), Ear Prick (EP) and Venous (VP) BGA haemoglobin

Table 3.35 describes the finger prick BGA haemoglobin compared to the venous laboratory EDTA haemoglobin for the healthy participant group, the patient group and the combined results. There were complete data sets in the healthy group but 2 incomplete sets for the patient group, which were due to 1 insufficient volume of collection and 1 laboratory report as not received. The mean bias for both groups were similar at 8.27g/l and 8.33g/l for the healthy group and diabetic group respectively, giving a combined mean of 8.32g/l. There

were wide LOA of -2.2g/l to 18.7 g/l and -4.84g/l to 21.5g/l for the healthy participant and patient groups respectively.

Participant group	Complete data set	Range of measurement g/l	Mean bias g/l	Standard Deviation of the bias (g/l)	Lower 95% LOA bias	Upper 95% LOA bias
Healthy Participants	23/23	112.4 -166.4	8.27	5.34	-2.20	18.7
Diabetic patients	46/48	81.6-172.6	8.33	6.72	-4.84	21.5
Combined	69/71	81.6-172.6	8.32	6.26	-3.95	20.6

Table 3. 35 Results of finger prick haemoglobin compared to venous laboratory EDTA samples in healthy participant group, patient group and combined results.

Table 3.36 compares the ear prick haemoglobin to the laboratory gold standard. The mean bias was consistently lower compared to the finger prick equivalents at 4.79g/l in the healthy participant group and 6.8g/l in the patient group with very similar 95% LOAs of -5.75g/l to 15.3g/l and -5.75g/l to 19.3 g/l respectively.

Participant group	Complete data set (g/l)	Range of measurement (g/l)	Mean bias (g/l	Standard Deviation of the bias (g/l)	Lower 95% LOA bias	Upper 95% LOA bias
Healthy Participants	22/23	102.5-160.8	4.79	5.38	-5.75	15.3
Diabetic patients	38/48	75.9-172.6	6.8	6.40	-5.75	19.3
Combined	60/71	75.9-172.6	6.06	6.08	-5.85	18.0

Table 3. 36 Results of Ear prick haemoglobin compared to venous laboratory EDTA samples in healthy participant group, patient group and combined results.

Table 3.37 describes the venous BGA haemoglobin compared to the venous laboratory EDTA haemoglobin. The mean bias suggested more concordance between this sampling modality

than either the finger prick or ear prick in both the healthy participant group (mean bias 1.43) and the patient group (mean bias 1.96g/l).

Participant group	Complete data set	Range of measurement g/l	Mean bias g/l	Standard Deviation of the bias (g/l)	Lower 95% LOA bias	Upper 95% LOA bias
Healthy Participants	23/23	103.1-152.6	1.43	2.72	-3.89	6.77
Diabetic patients	47/48	74.5-165	1.96	3.57	-5.04	8.96
Combined	70/71	74.5-165	1.79	3.31	-4.69	8.27

Table 3. 37 Results of Venous BGA haemoglobin compared to venous laboratory EDTA samples in healthy participant group, patient group and combined results.

Figure 3.29 shows the Bland-Altman plot of the finger prick haemoglobin compared to the laboratory result for healthy participants. The mean difference and 95 % LOA demonstrated the discordance between the sampling modalities, exceeding the set limits of <5g/l.

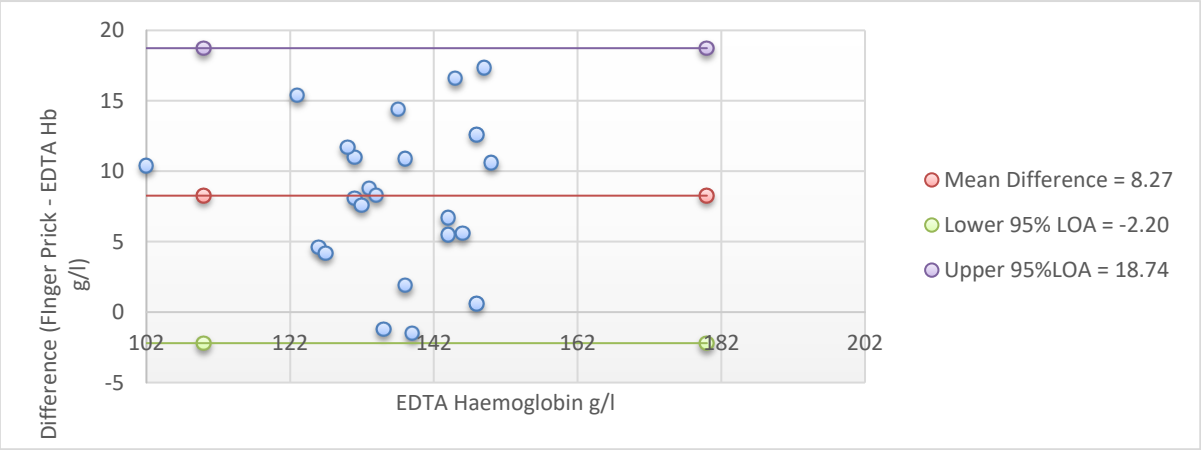


Figure 3. 29 Bland-Altman Plot for finger prick haemoglobin results compared to laboratory EDTA haemoglobin in healthy participants.

Similarly, the finger prick result from patients (shown in figure 3.30) demonstrated discordance from the laboratory results, with 95% LOA exceeding the 5g/l limits. The figure

demonstrates an outlying result which was approximately 30g/l removed from the gold standard.

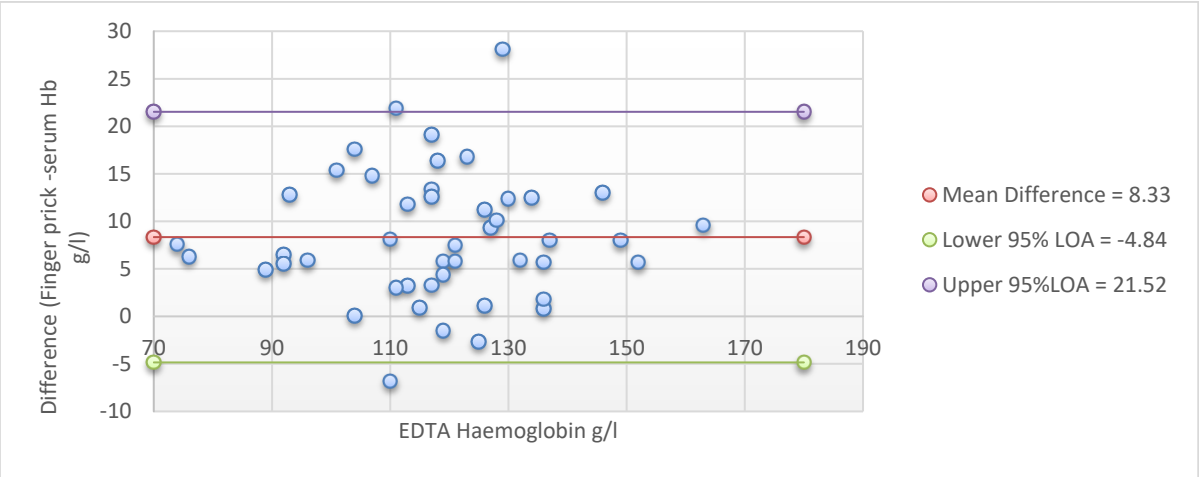


Figure 3. 30 Bland-Altman Plot for finger prick haemoglobin results compared to laboratory EDTA haemoglobin in acutely unwell diabetic patients.

The combined healthy participant and patient results for finger prick BGA are shown in figure 3.31. There was significant discordance between the sampling modalities, exceeding the set criteria.

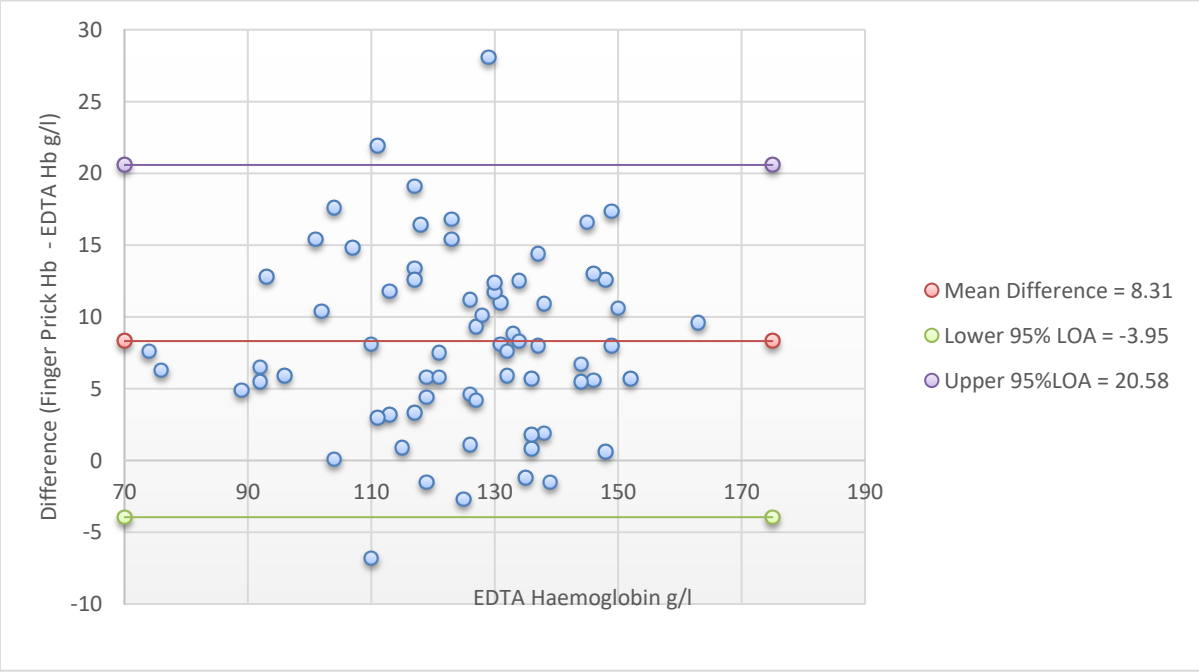


Figure 3. 31 Bland-Altman Plot for finger prick haemoglobin results compared to laboratory EDTA haemoglobin in healthy participants and acutely unwell diabetic patients combined.

Figure 3.32 shows the Bland Altman plot for ear prick haemoglobin compared with the laboratory result in healthy participants. There was significant discordance in results with the 95% LOA greater than the 5g/l.

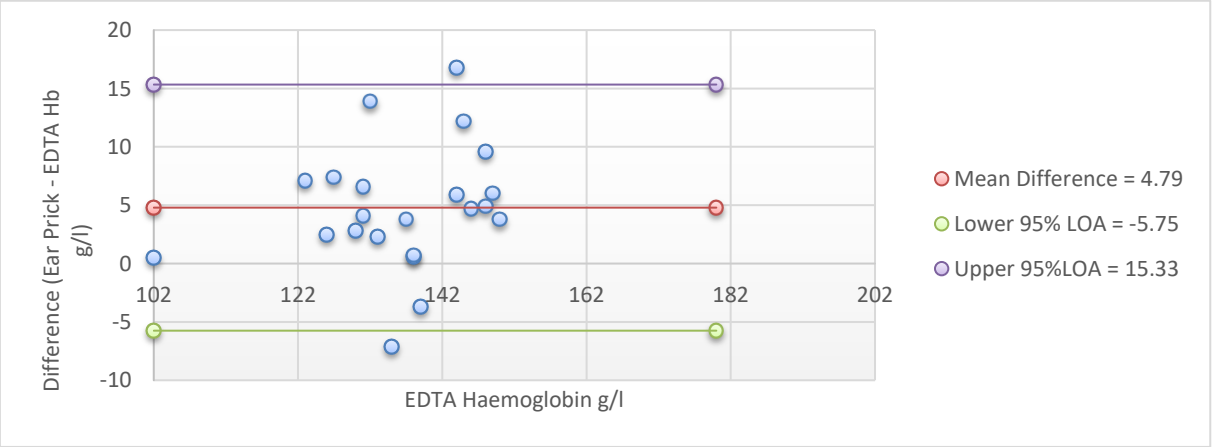


Figure 3. 32 Bland-Altman Plot for ear prick haemoglobin results compared to laboratory EDTA haemoglobin in healthy participants.

Figure 3.33 shows the Bland Altman plot for ear prick haemoglobin compared with the laboratory result in patients. There was also significant discordance in results with the 95% LOA greater than the 5g/l.

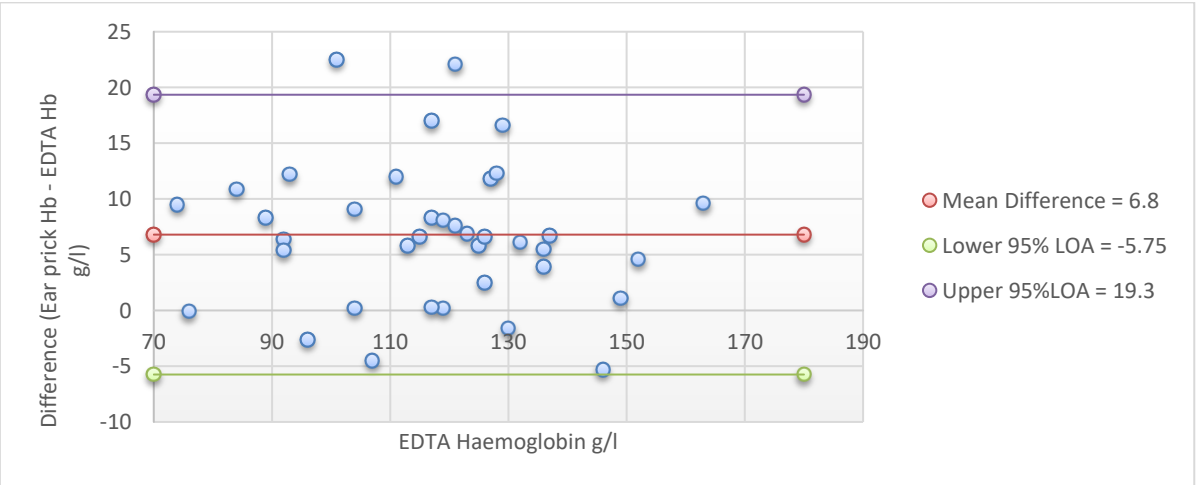


Figure 3. 33 Bland-Altman Plot for ear prick haemoglobin results compared to laboratory EDTA haemoglobin in acutely unwell diabetic patients.

The combined ear prick results in figure 3.34 demonstrated the spread of results across a range of haemoglobins, including many participants who were anaemic, up to the upper end of the normal range. On average, the ear prick sample was greater compared to the laboratory gold standard, with only 6 results being lower than the laboratory equivalent. Once again, there was significant discordance between the ear prick and laboratory sample.

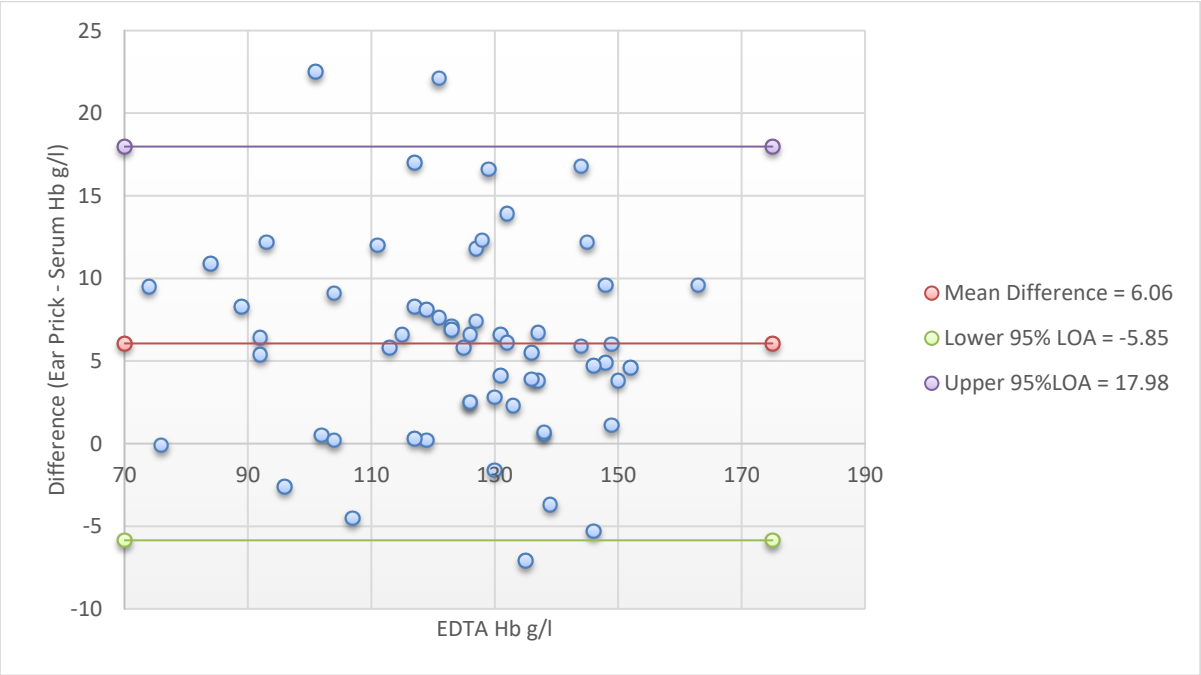


Figure 3. 34 Bland-Altman Plot for ear prick haemoglobin results compared to laboratory EDTA haemoglobin in healthy participants and acutely unwell diabetic patients combined (Figure 3.34).

Finally, a venous sample (assessed using the BGA) was compared to the laboratory haemoglobin result. The Bland Altman plots demonstrate that the acceptability criteria were not reached for healthy controls (see figure 3.35), patients (see figure 3.36) or when groups were combined (see figure 3.37).

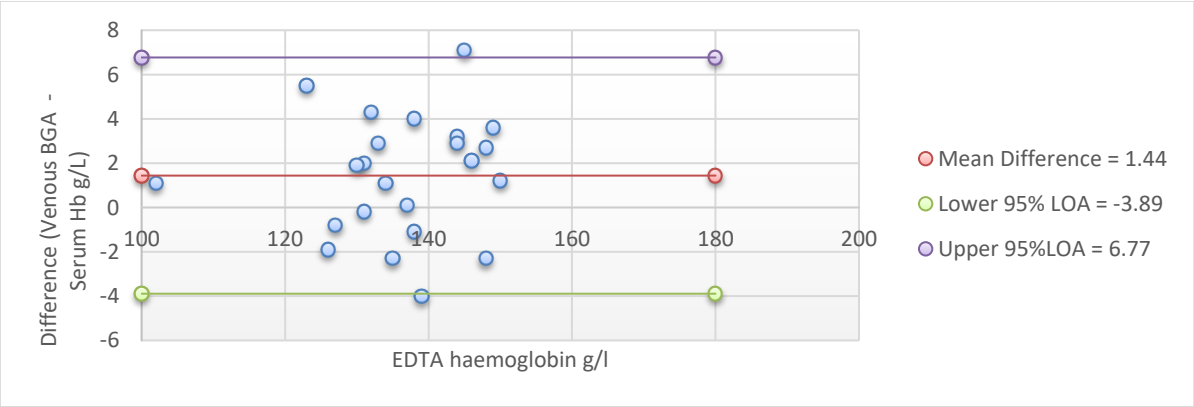


Figure 3. 35 Bland-Altman Plot for Venous BGA haemoglobin results compared to laboratory EDTA haemoglobin in healthy participants.

Figure 3.36 displays patient data, and as expected, included a wider range of haemoglobin measurements than seen in healthy subjects.

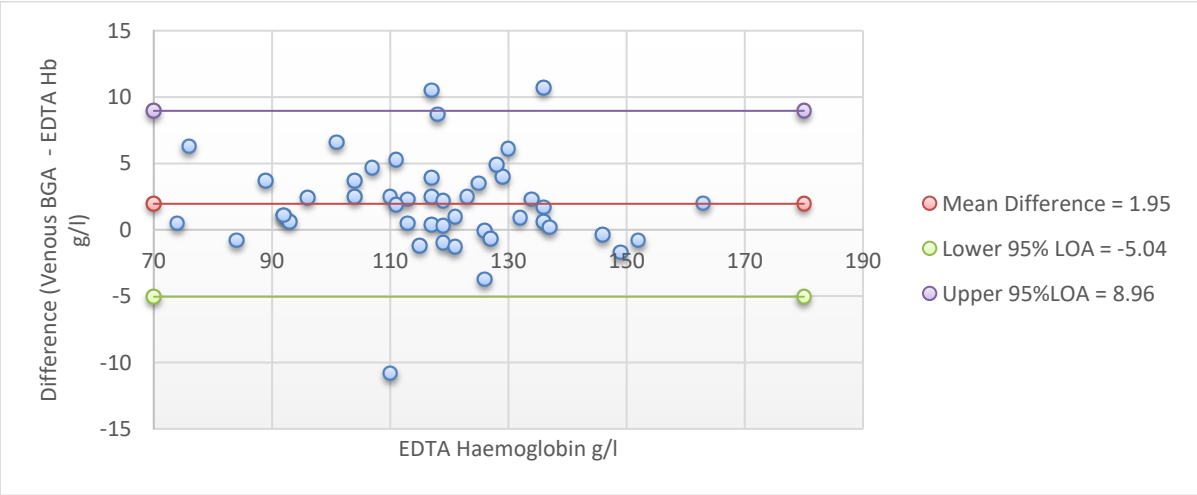


Figure 3. 36 Bland-Altman Plot for Venous BGA haemoglobin results compared to laboratory EDTA haemoglobin in acutely unwell diabetic patients.

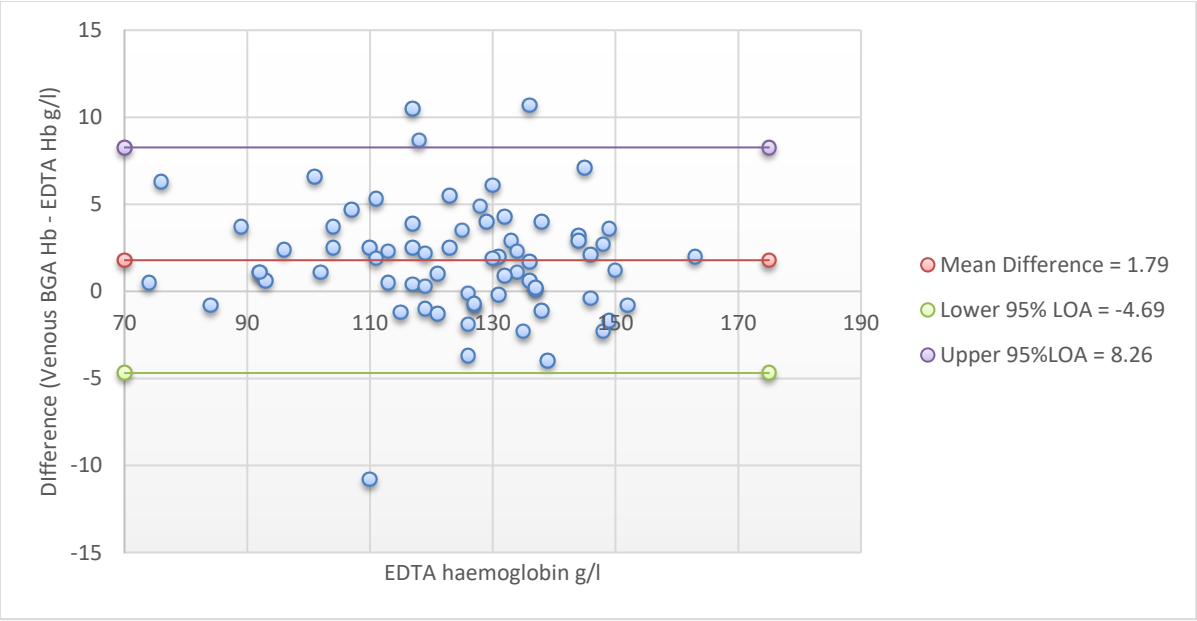


Figure 3. 37 Bland-Altman Plot for Venous BGA haemoglobin results compared to laboratory EDTA haemoglobin in healthy participants and acutely unwell diabetic patients combined.

Results compared to acceptability criteria

The acceptability criteria for haemoglobin state 95% of results should fall within 5 g/l of the EDTA sample (see section 2.4.2). Table 3.38 below shows the results for the number and percentage of samples that fulfil these criteria for each sampling method. Only approximately a quarter of the finger prick samples and less than half of the ear prick samples fulfilled this criterion, with venous BGA approaching 86% of samples reaching this acceptability criterion with less than half of the ear prick and approximately a quarter of the finger prick samples fulfilling this cut off.

	FP %	EP %	VP %
Healthy	26.3	48.1	89.6
Patient	28.6	35.6	77.7
Combined	28.1	39.6	81.4

Table 3. 38 The estimated percentage of samples meeting the acceptability for haemoglobin for Finger prick (FP), Ear prick (EP) and Venous BGA (VP) in healthy, patient and combined groups

Comparison between groups

Table 3.39 below shows the results of the Friedman's test when the MEs between each of the methods of testing were compared (Finger prick, ear prick and venous prick). There were significant differences between the biases between these groups with chi-squared value of 51 and p value of 0.000.

Test Statistics	
N	59
Chi-Square	51.034
df	2
Asymp. Sig.	.000

Table 3. 39 Results of Friedman's test between finger prick, ear prick and venous BGA ME results

Post Hoc analysis is show in table 3.40 below. This shows that there were statistically significant differences between the biases of both the capillary sampling methods (Finger prick and ear prick) when compared to the venous BGA MEs (p values <0.001), however, there were no significant difference between the two capillary methods (p=0.92). Here, the venous BGA haemoglobnin showed reduced bias compared to both finger prick and ear prick.

	EP - FP	VP - FP	VP - EP
Adjusted Significance	.092	<0.001	<0.001

Table 3. 40 Post hoc analysis of ME results between Finger prick (FP), ear prick (EP) and venous BGA (VP) using Wilcoxan signed ranks test.

The results of the F tests of the MEs for haemoglobin are shown in table 3.41 and 3.42 below. There were no statistically significant differences between the range of LOAs between the healthy and patient groups in any of the testing methods. There was also no significant difference between the finger prick and ear prick sampling methods (p=0.823).

When both the capillary samples (finger prick and ear prick) were compared to the venous BGA samples there were significant differences, with the venous BGA having significantly narrower LOAs (p values <0.001).

	FP	EP	VP
Healthy to patient	0.244	0.399	0.168

Table 3. 41 Results of F-tests of the biases in haemoglobin results between healthy and patient groups for Finger prick (FP), Ear prick (EP) and venous BGA (VP).

	F test Result
FP to EP	0.823
FP to VP	<0.001
EP to VP	<0.001

Table 3. 42. Results of F-tests of the biases in haemoglobin results between Finger prick (FP), Ear prick (EP) and venous BGA (VP).

Comparison of results by age

Mean bias results were studied by quintile groups, as shown in table 3.43. There was no clear pattern between increasing age and mean bias.

	Healthy				Patient Group			
Quintile	Age Range of Quintile	Mean Bias g/l			Age Range of quintile	Mean bias g/l		
		FP	EP	VP		FP	EP	VP
1st	24 - 25	11.1	2.6	1.33	19-53.8	8.71	4.46	2.03
2nd	25 - 28.2	9.96	8.32	2.92	53.8-63	8.52	7.14	0.78
3rd	28.2 - 35.4	9.22	7.22	2.7	63-74	7.03	7.05	2.5
4th	35.4 - 42	-0.42	5.56	2.43	74-82	5.85	11.89	1.94
5th	42 - 49	5.56	1.9	-0.44	82-87	11.7	6.37	2.68

Table 3. 43 Comparison of mean bias for haemoglobin when divided into age quintile groups in healthy group and patient group for finger prick (FP), ear prick (EP) and venous BGA (VP) testing methods

There were no significant differences between the quintiles for each of the groups (p values 0.269, 0.492 and 0.161) for finger prick, ear prick and venous BGA results respectively, when compared using Kruskal Wallis test.

Summary

None of the BGA samples showed sufficient concordance to satisfy the acceptability criteria of 95% of the values being within 5g/l for haemoglobin. The venous sample showed the closest level of concordance where 95% of the values were within 10g/l and showed statistically higher levels of accuracy and narrower limits of agreement when directly compared to the other sampling methods. The ear prick and finger prick showed no significant differences in their accuracy between one another

3.4.5 Lactate

Tables 3.45 to 3.47 describe the results for lactate, where finger and ear prick samples were compared to venous BGA standard. The Bland-Altman plots and regression plot for the corresponding data are given in figures 3.38-3.43.

Table 3.39 describes the normality testing which demonstrates that the finger and ear prick sampling did not conform to a normal distribution.

	Kolmogorov-Smirnov			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
FP Bias	0.171	71	0	0.905	71	0
EP Bias	0.139	62	0.005	0.908	62	0

Table 3. 44 Normality testing of the MEs for Finger Prick (FP) and Ear Prick (EP) lactate

Table 3.45 describes finger prick compared to venous BGA lactate. As the distribution of the MEs were not normally distributed, Bland-Altman LOAs are not valid and not given. The

variability of the MEs suggested a low degree of agreeability with the combined standard deviation being 0.34mmol/l.

Participant group	Complete data set	Range of measurement mmol/l	Mean bias mmol/l	Standard Deviation of the bias (mmol/l)
Healthy Participants	23/23	0.7-1.7	0.091	0.26
Diabetic patients	48/48	0.5-5.4	-0.040	0.369
Combined	71/71	0.5-5.4	0.0028	0.342

Table 3. 45 Results of finger prick lactate compared to venous BGA lactate in healthy participant group, patient group and combined results.

Figure 3.38 below shows the scatter plot of the combined healthy participant and patient group results for finger prick lactate. As venous BGA lactate increased, there was a progressive tendency for the finger prick result to underestimate the lactate values. In light of this, the degree of difference could not be predicted by a single value for the upper and lower 95 % limits of agreement and therefore linear regression analysis was used for this group (as described in section 2.6 of the methods).

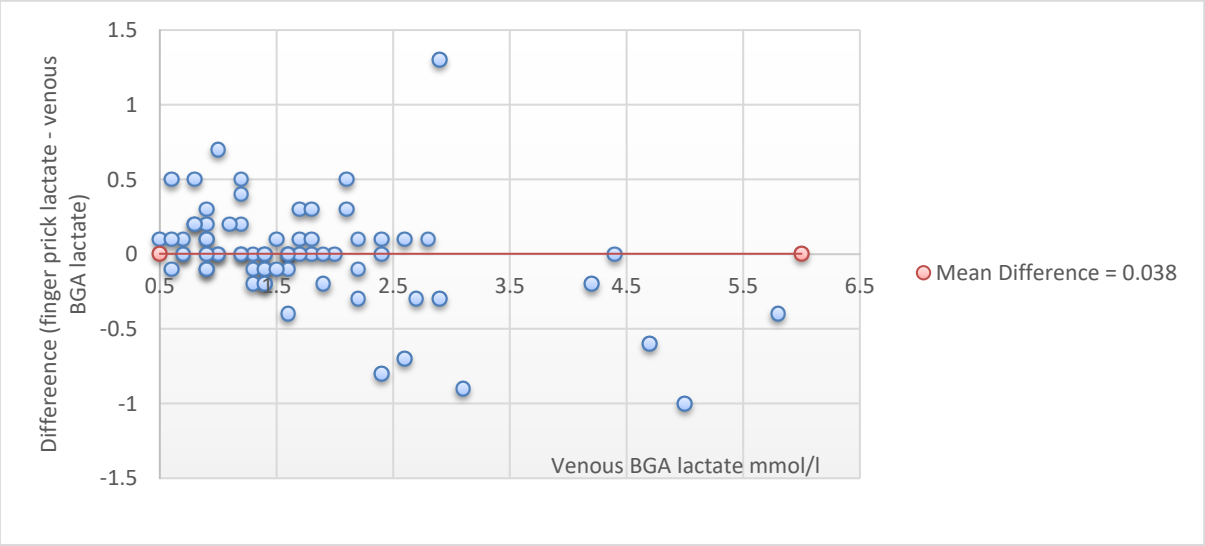


Figure 3. 38 Scatter Plot for finger prick lactate results compared to venous BGA lactate in healthy participants and acutely unwell diabetic patients combined.

Table 3.46 describes the finger prick compared to venous BGA lactate in healthy participants and patients following linear regression analysis. The predicted mean values and upper and lower 95% confidence intervals (CI) have been included in the table to cover the lower and upper range of the lactate results. This provides the maximum and minimum range of the predicted means and upper and lower 95% CIs. For the healthy group the predicted mean bias was 0.149 when the VBG lactate was 0.7mmol/l (the lowest venous BGA level recorded in this group). At the top of the range (when the venous BGA lactate was 1.7mmol/l) the predicted mean bias was 0.0106mmol/l; so the predicted mean bias decreases in this group as the lactate level increased (but remained within the normal range). The 95 % confidence intervals (equivalent to the LOA) similarly decrease with increasing lactate ranging from -0.473mmol/l to 0.769mmol/l when the lactate was 0.7mmol/l to -0.618mmol/l to 0.673mmol/l at 1.7mmol/l when the lactate reached 1.7mmol/l. The lactate values increased in the patient group, and the bias continued to decrease until it became negative when the venous BGA lactate was 5.4mmol/l, with a predicted mean bias of -0.5.

Participant group	Range of measurement mmol/l	Predicted mean bias at corresponding range measurement	Lower 95% Confidence interval	Upper 95% Confidence interval
Healthy Participants	0.7 1.7	0.149 0.0106	-0.473 -0.618	0.769 0.637
Diabetic patients	0.5 5.4	0.176 -0.5	-0.444 -1.15	0.796 0.149
Combined	0.5 5.4	0.176 -0.5	-0.444 -1.15	0.796 0.149

Table 3. 46 Results of finger prick lactate compared to venous BGA lactate in healthy participant group, patient group and combined results showing predicted mean bias, lower and upper 95% confidence interval following linear regression analysis.

Figure 3.39 shows the scatter chart of the finger prick lactate bias compared to venous BGA lactate values. The linear regression lines for both the upper and lower 95% confidence interval and the predicted mean are included. These demonstrate that finger prick lactate measurement increasingly under-predicted the venous BGA lactate as this value increased. When venous BGA lactate was less than 2mmol/l (and within the normal range) the lactate measurement still did not fit the aim of 95% of values being within 0.5mmol/l.

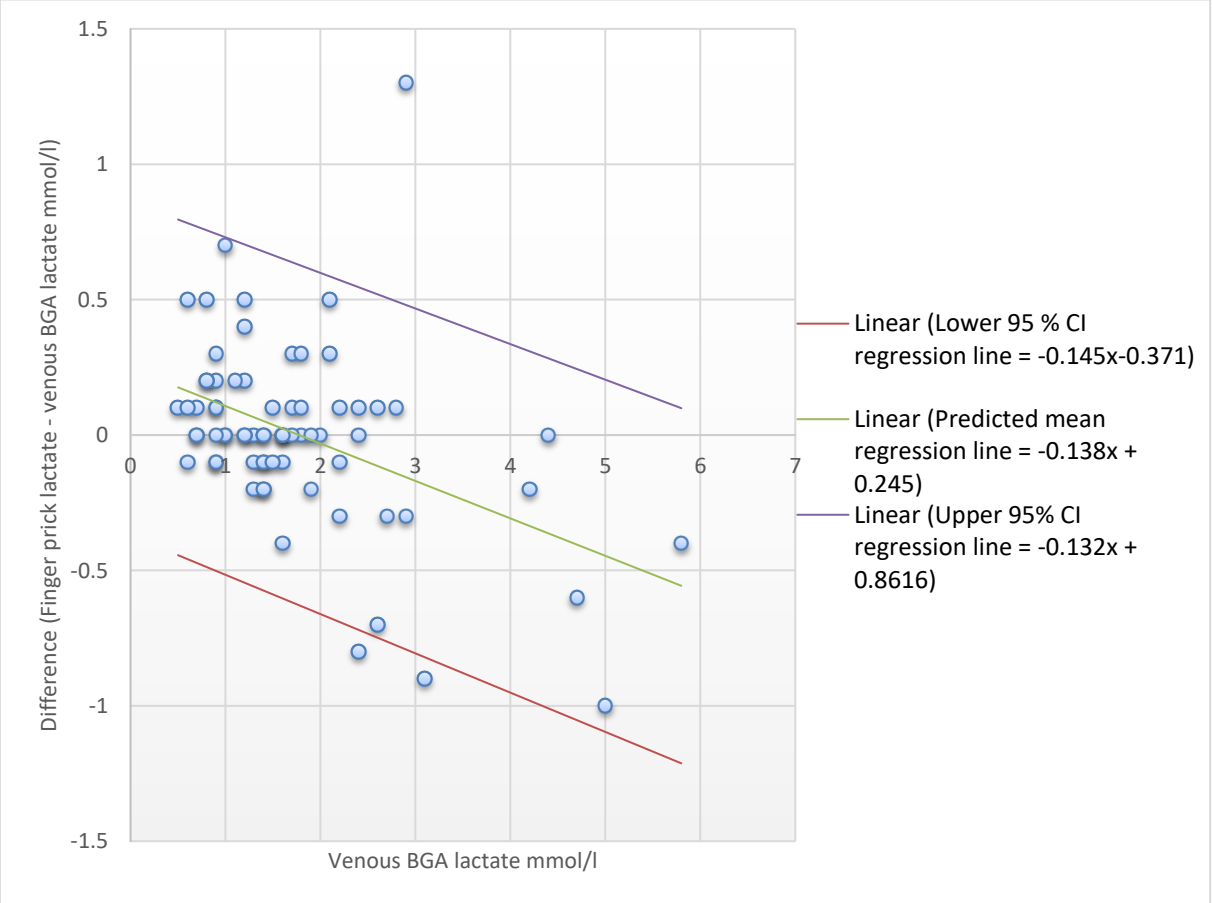


Figure 3. 39. Scatter chart of finger prick lactate bias compared to venous BGA lactate with linear regression lines showing the predicted mean and the 95% confidence intervals (CI)

Ear prick lactates were then compared to the venous BGA lactate result, and are shown below. The normality testing suggested the distribution was not normal (described in table 3.47). There was incomplete data capture from both the healthy participant and patient

group due to insufficient volumes of the capillary blood. The mean difference was similar in both healthy and patient groups (-0.17mmol/l and 0.11mmol/l respectively) however, these are lower than that of the finger prick group. With a larger standard deviation the combined 95% LOA were relatively wide (-0.964 to 0.693).

Participant group	Complete data set	Range of measurement mmol/l	Mean bias mmol/l	Standard Deviation of the bias (mmol/l)	Lower 95% LOA bias	Upper 95% LOA bias
Healthy Participants	21/23	0.3-2.1	-0.17	0.362	-0.877	0.543
Diabetic patients	41/48	0.4-5.2	-0.11	0.454	-1.01	0.770
Combined	62/71	0.3-5.2	-0.14	0.423	-0.964	0.693

Table 3. 47 Results of Ear prick haemoglobin compared to venous BGA lactate in healthy participant group, patient group and combined results.

The 95% LOAs were compared to the weighted average centile values (as per section 2.6 of the methods) as the distribution did not fit with linear regression modelling. This gave an upper 95% confidence interval of 0.745 and a lower CI of -1.14, wider than those calculated based on a normal distribution as shown in table 3.20. In light of this, the LOAs described for this parameter are likely to suggest a higher degree of agreeability for this test than is actually present.

Figure 3.40 describes a Bland-Altman plot for the ear prick BGA lactate compared to the venous BGA results. The 95% LOA did not meet the required criteria of 95% LOAs <0.5mmol/l.

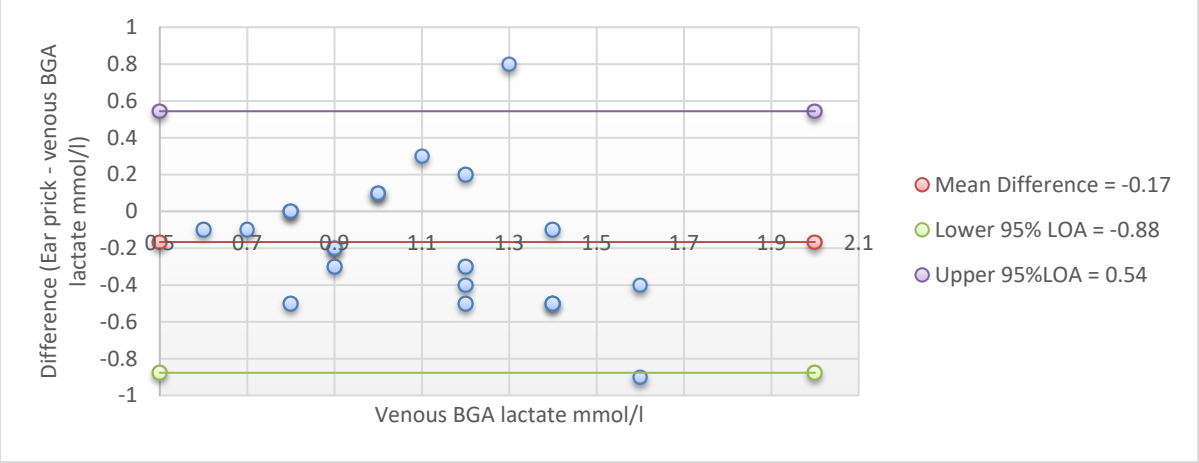


Figure 3. 40 Bland-Altman Plot for ear prick haemoglobin results compared to laboratory EDTA haemoglobin in healthy participants.

Figure 3.41 shows the patient ear prick BGA lactate compared to the venous BGA results. These include some results outside of the normal range (>2mmol/l). The mean differences and 95% LOA were similar to that of the healthy group with a negative mean difference and LOA failed to meet the agreed acceptability criteria.

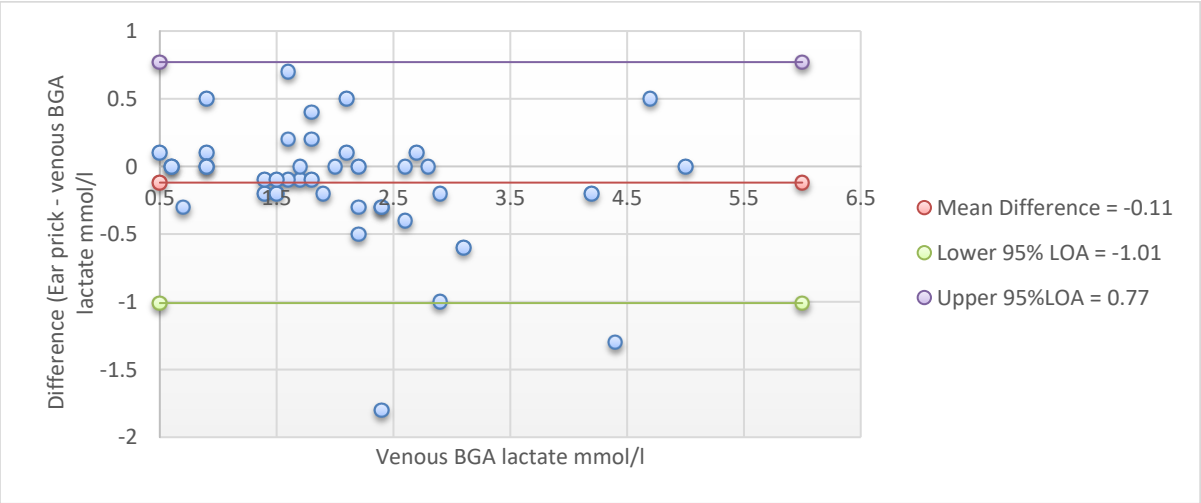


Figure 3. 41 Bland-Altman Plot for ear prick haemoglobin results compared to laboratory EDTA haemoglobin in acutely unwell diabetic patients.

The combined healthy control and patient ear prick results are shown in figure 3.42, including an outlying result which differed by 1.8 mmol/l to the corresponding venous BGA result. There was not the same degree of progressively negative bias with increasing lactate values, as was seen with finger prick samples.

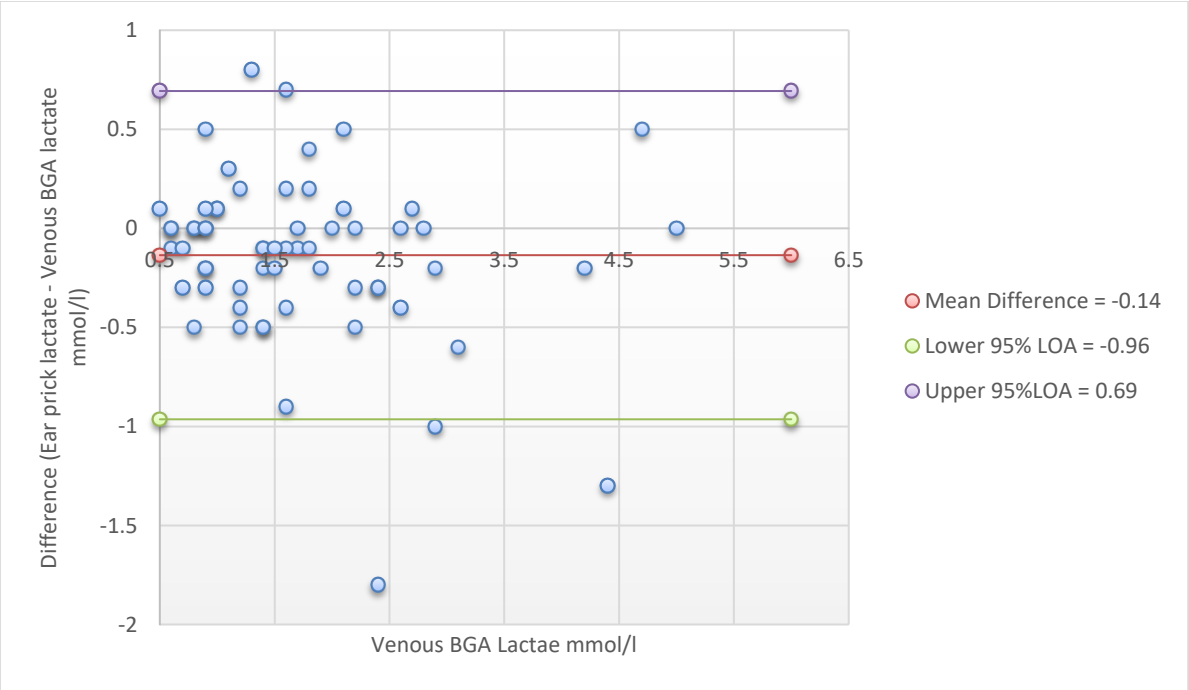


Figure 3. 42 Bland-Altman Plot for ear prick haemoglobin results compared to laboratory EDTA haemoglobin in healthy participants and acutely unwell diabetic patients combined.

Results compared to acceptability criteria

The acceptability criteria for lactate state 95% of results should fall within 0.5 mmol/l of the venous BGA sample (see section 2.4.2). Table 3.43 below shows the results for the number, percentage and confidence limits of samples that fulfil these criteria for each sampling method. Approximately 85% (CI 74-92%) of the finger prick sample and three quarters (CI 66-87%) of the ear prick samples meet these criteria.

	FP / total	FP %	95% Confidence Limits	EP / total	EP %	95% Confidence Limits
Healthy	19/23	82.6	61-95	15/21	71.4	48-89
Patient	41/48	85.4	72-94	33/41	80.5	62-91
Combined	60/71	84.5	74-92	48/62	77.4	66-87

Table 3. 48 The number and percentage of samples meeting the acceptability for lactate for Finger prick (FP) and Ear prick (EP) in healthy, patient and combined groups

Comparison between groups

Table 3.43 below shows the results of the Wilcoxon Signed Ranks test when the MEs of the finger prick and ear prick were compared. There were significant differences between the MEs of these groups with a p value of 0.11, with finger prick sampling having a significantly reduced level of bias compared to ear prick tests.

Test Statistics	
Asymp. Sig.	.011

Table 3. 49 Results of Wilcoxon Signed Ranks test between finger prick and ear prick lactate ME results

The results of the F tests of the MEs for lactate are shown in table 3.50 and 3.51 below. There were no statistically significant differences between the range of LOAs between the healthy and patient groups in any of the testing methods or between the sampling methods themselves when patients and healthy subjects were combined (p=0.088).

	FP	EP
Healthy to patient	0.093	0.280

Table 3. 50 Results of F-tests of the MEs in lactate results between healthy and patient groups for Finger prick (FP), Ear prick (EP) and venous BGA (VP).

	F test Result
FP to EP	0.088

Table 3. 51. Results of F-tests of the MEs in lactate results between Finger prick (FP), Ear prick (EP) and venous BGA (VP).

Comparison of results by age

Parameters bias was studied by age quintile groups, as shown in table 3.52. There was no pattern between increasing age and changes to mean bias.

	Healthy			Patient Group		
Quintile	Age Range of Quintile	Mean Bias g/l		Age Range of quintile	Mean bias g/l	
		FP	EP		FP	EP
1st	24 - 25	0.35	-0.033	19-53.8	-0.09	-0.08
2nd	25 - 28.2	0.2	-0.13	53.8-63	-0.14	-0.29
3rd	28.2 - 35.4	-0.02	-0.06	63-74	0.01	-0.1
4th	35.4 - 42	0.48	0.08	74-82	-0.06	0.043
5th	42 - 49	-0.1	-0.42	82-87	0.09	-0.16

Table 3. 52 Comparison of mean bias for lactate when divided into age quintile groups in healthy group and patient group for finger prick (FP) and ear prick (EP) testing methods

There were no significant differences between the quintiles for either the finger prick or ear prick groups (p= 0.328 and 0.445 respectively).

Summary

Neither the finger prick nor ear prick lactate results were sufficiently comparable to the venous BGA gold standard as per the defined criteria of 95% of the values being within 0.5mmol/l. Despite this, when the two methods were compared, finger prick tests showed significantly more accuracy than the ear prick with approximately 85% of results satisfying the acceptability criteria.

3.5 Experience rating

Table 3.53 describes the scores from the visual analogue scales for each of the healthy group, patient group and the combined results. In the healthy group the median pain score was less for both the finger prick and ear prick when compared to the venepuncture and

there was no statistically significant difference between the pain scores of either of the capillary sampling method when compared to the venepuncture. In the patient group, however, finger prick and ear prick were both scored significantly lower than the venepuncture blood tests with a median of 0.45 for the finger prick and 0.35 for the ear prick compared to the venepuncture of 1.4. When the results of the two groups are combined both the ear prick and the finger prick were significantly less painful than the venepuncture (p value 0.00).

		Finger Prick	Ear Prick	Venepuncture
Healthy	Median	1.2	0.8	1.3
	Interquartile Range	0.5-1.9	0.2-1.5	0.4-1.8
	Significant difference compared to VP	No (p=0.295)	No (0.058)	-
Patient	Median	0.45	0.35	1.4
	Interquartile Range	0-1.5	0-1.7	0-3.53
	Significant difference compared to VP	Yes (p<0.001)	Yes (p=0.001)	-
Combined	Median	0.7	0.5	1.4
	Interquartile Range	0-1.55	0-1.50	0-2.80
	Significant difference compared to VP	Yes (p<0.001)	Yes (p=0.001)	-

Table 3. 53 The median, interquartile range and significant difference results for pain scores (out of a maximum of 10) for finger prick, ear prick and venepuncture (VP) in the healthy group, patient group and the healthy and patient group combined

The patient group were also asked which sampling modality they preferred, as shown in table 3.54. The majority of patients preferred the finger prick to the other modality with 60 % suggesting this as a preferred method. The ear prick was the next most commonly preferred modality with 17% preferring this method, with venepuncture being the least commonly preferred option.

Modality preference	Number of patients	Percent
Finger	29	60
Ear	8	17
Venous	6	13
No preference	1	2
Unable	4	8

Table 3. 54 Patient preference for modality of blood sampling

Table 3.55 below shows the number of attempts required per test. Data collection on number of attempts required started after the commencement of the validation part of the study so only includes 14 healthy participants. The finger and ear prick were both successful on the first attempt in more than 90% of the time whereas the ear prick was only successful on the first attempt approximately a third of the time with approximately 20 % requiring more than 3 attempts and 8% not successful despite more than 3 attempts.

	Modality	First attempt % (number)	Second Attempt % (number)	Third Attempt % (number)	More than 3 attempts % (number)	Number unsuccessful % (number)
Healthy	Finger	93 (13)	7 (1)	0 (0)	0 (0)	0 (0)
	Ear	21 (3)	29 (4)	29 (4)	14 (2)	7 (1)
	Venous	100 (14)	0 (0)	0 (0)	0 (0)	0 (0)
Patient	Finger	92 (44)	6 (3)	2 (1)	0 (0)	0 (0)
	Ear	33 (16)	21 (10)	17 (8)	21 (10)	8 (4)
	Venous	87 (42)	13 (6)	0 (0)	0 (0)	0 (0)
Combined	Finger	92 (57)	6 (4)	2 (1)	0 (0)	0 (0)
	Ear	31 (19)	23 (14)	19 (12)	19 (12)	8 (5)
	Venous	90 (56)	10 (6)	0 (0)	0 (0)	0 0)

Table 3. 55 The number of attempts required for each modality in the healthy group, patient group and combined groups.

4. Discussion

4.1 Summary of results

This is the first study to assess the accuracy and acceptability of capillary blood tests when assessed in a blood gas analyser for glucose, sodium, potassium, haemoglobin and lactate. It is the first study to compare their accuracy to the gold standard laboratory samples but also to venous samples processed in a blood gas analyser. Table 4.1 below summarises the results for each parameter comparing the results to the acceptability criteria. It also ranks the methods in order of accuracy as per the Friedman's or Wilcoxon signed ranks test.

	Sampling method	Mean Bias	Limits of Agreement	Acceptability Criteria met	% Meeting Acceptability Criteria	Rank
Glucose mmol/l (%)	Finger prick	0.26 (3.81%)	-1.91– 2.43mmol/l	No*	87.4	1
	Ear Prick	0.46 (9.11%)	18.8% - 29.4%	No	68.1	3
	Venous BGA	0.23 (3.13%)	8.94%-20.6%	Yes**	96.5	1
Sodium mmol/l	Finger prick	1.37	-1.79 – 4.52	No	94.8	3
	Ear Prick	0.88	-2.52 – 4.27	Yes	96.5	1
	Venous BGA	0.92	-1.92 – 3.77	Yes	98.2	1
Potassium mmol/l	Finger prick	-0.191	-0.695 – 0.312	No	88.0	2
	Ear Prick	-0.011	-0.762 – 0.740	No	80.8	1
	Venous BGA	-0.394	-0.793 – 0.004	No	69.8	3
Hb g/l	Finger prick	8.32	-3.95 -20.6	No	28.1	2
	Ear Prick	6.06	-5.85 - 18	No	39.6	2
	Venous BGA	1.79	-4.69 – 8.27	No	81.4	1
Lactate mmol/l	Finger prick	- 0.5 to 0.176	Not valid	No	84.5 (CI 74-92)	1
	Ear Prick	-0.14	-0.964 – 0.693	No	77.4 (CI 66-87)	2

*Table 4. 1 Comparison of mean bias, limits of agreement, whether the acceptability criteria were met and ranking of samples according to their accuracy (1 most accurate 3 least) for each parameter and testing modality. *Acceptability criteria met when glucose >12mmol/l.**Acceptability not met in the healthy group when glucose <10mmol/l*

4.1.1 Glucose

All glucose BGA samples tended to overestimate the plasma glucose with mean bias ranging from 0.2 to 0.7mmol/l. In this population, capillary finger prick, ear prick and venous BGA results were not sufficiently accurate in the normal physiological range to be adopted for use in clinical care when compared to the ISO guidelines for glucose meters. The finger prick and venous BGA samples were sufficiently accurate in the hyperglycaemic range when the plasma glucose was above approximately 12mmol/l. There was no significant difference in the accuracy of the venous BGA test and the finger prick test but both these methods were significantly more accurate than the ear prick method.

The ear prick sample consistently demonstrated poorer agreement with the gold standard test than either the finger prick or the venous BGA sample and less reliability with wider limits of agreement. There were technical difficulties in obtaining adequate samples and the frequent requirement for several capillary punctures. This might have led to haemolysis or clot formation. Because of these difficulties several samples were not able to be processed by the BGA or were not obtainable at all.

Impact of results on management of acutely unwell adults

Given that the results show suitable accuracy in patients in the hyperglycaemic range, when glucose is above 12, finger prick BGA glucose could be used as an alternative to standard

testing when managing patients who may be within this range. This maybe particularly useful in patients being treated for diabetic emergencies such as DKA or hyperglycaemic hyperosmolar non-ketotic states when regular assessment of several parameters may be important. Below this range finger prick samples show similar accuracy to what has been seen in glucose meter and arterial BGA samples in critically ill adults on intensive care (Inoue S 2013), however, do not meet the ISO guidelines so should only be used with caution.

4.1.2 Sodium

This is the first study to show the accuracy of capillary sodium samples analysed in a blood gas analyser. It is also one of the first studies to compared venous BGA results alone (excluding arterial samples).

In the current study, finger and ear prick BGA results had a positive mean bias of 1.37mmol/l and 0.92mmol/l respectively. The limits of agreement for both sampling modalities were marginally outside those required by the US CLIA requirement of 95% of $\leq$4mmol/l (FederalRegister 1992). Despite this when the proportion of samples meeting this criteria is calculated the ear prick samples satisfy the US CLIA guidelines with 96.5% fulfilling this criteria and finger prick samples only fail to reach the criteria by only 0.2% (94.8% fulfil the criteria). The venous BGA samples met the US CLIA requirements with LOAs within the 4mmol/l cut off.

Impact of results on management of acutely unwell adults

The current study supports the use of venous BGA sodium and ear prick sodium as an alternative to venous laboratory serum samples. The finger prick capillary BGA sample, however, only marginally failed to reach the accuracy level required by the US CLIA guidelines but may still be seen as clinically acceptable given its proximity to the required accuracy. NICE guidelines for the management of hyponatraemia state mild hypoglycaemia is in the range of 130-135mmol/l. The lower range LOA for the finger prick sample is -1.79 and upper 4.52 and ear prick -2.52 and 4.27. The recommendations from NICE would be to repeat a sample when sodium is within the mild ranges. The impact of a test falling at the extreme ranges of LOAs would be to be potentially falsely reassured by a normal result when only mild hyponatraemia exists and this is unlikely to have a large impact on acute clinical care (NICE 2015). It may be suitable to use this method for monitoring sodium with the addition of venous testing when results are abnormal.

4.1.2 Potassium

This is the first study to compare capillary and venous BGA potassium to the gold standard serum and demonstrated that neither capillary nor venous BGA samples meet the US CLIA guidelines of 95% of the samples within 0.5mmo/l of the gold standard (FederalRegister 1992). The guideline criteria could be met using finger prick and venous BGA samples following correction using the mean bias.

All BGA values under-estimated the potassium concentration when compared to the laboratory result. Potassium is predominantly an intracellular ion, released during haemolysis. The under-estimation may reflect potassium release from the laboratory sample during transit and analysis, rather than true physiological change or BGA error. Furthermore, serum samples have higher potassium concentrations (by 0.36 +/- 018mmol/l (Jaya R Asirvatham 2013) compared with plasma samples due clotting-associated potassium release from platelets. This reported difference is a very similar to that which was seen in the whole blood venous BGA result in the current study, where haemolysis or clotting is likely to be minimal.

The potassium sample for the finger prick was the only sample to show any significant differences in mean difference between the quintiles. In both the healthy and patient group the mean bias in the 1st quintile were higher than the other quintile groups. There did not appear to be any evidence of specific changes in mean bias across the ranges of age. The cause for this is not clear, however, may be due to the younger patients being sampled earlier in the study when the technique of the investigator may have caused a higher degree of haemolysis.

Impact of results on management of acutely unwell adults

It is common place to monitor the correction of electrolytes, and especially potassium in patients with hyperkalaemia, using serial samples analysed by BGA for example in recent

DKA guidelines (Group 2014) which advocate venous BGA potassium monitoring with intermittent laboratory confirmation. Given that the current study shows venous capillary BGA potassium is more accurate when compared to venous BGA sample, this method would be a more favourable alternative. The recommendations for the use of venous BGA sampling may have the potential to significantly underestimate potassium with the lower 95% up to 0.8mmol/l away from the gold standard sample (similar to what has previously been reported) with only approximately three quarters of results fulfilling the US CLIA criteria. This has the potential of falsely diagnosing patients with severe hypokalaemia despite potassium being measured with in the normal range or give falsely reassuring level for patients in the hyperkaleamic range. Use of finger prick samples may reduce this risk but cautious use when samples are outside or at the extremes of the normal range when laboratory confirmation should be applied. Given the wide LOAs seen in the ear prick sample and hence poor reliability it may be preferable to use finger prick capillary samples when compared to ear prick.

4.1.3 Haemoglobin

This is the first study to compare capillary haemoglobin measured in a BGA to laboratory samples. Neither the capillary samples nor the venous BGA sample showed sufficient levels of accuracy, predetermined to be $\leq$5g/l of the EDTA laboratory samples. All samples showed a positive bias. The ear and finger prick samples demonstrated an upper LOA approaching 20 g/l

Impact of results on management of acutely unwell adults

The level of error reported in the current study may prohibit the use of BGA results in informing clinical care in patients unless treatment could be based on an approximate value. Indeed, previous studies have concluded that haemoglobin BGA were not sufficiently accurate for clinical care. Previous studies looking at haemoglobin measured by capillary samples have compared the results of haemocue test to laboratory Haemoglobin and these have also shown capillary samples to be less accurate compared to venous and arterial samples measured using the same methodology and not sufficiently accurate to guide transfusions (Seguin P1 2010, Sanchis-Gomar 2013). One specific study where LOAs were reported described LOAs between -13 g/l to 17 g/l (Seguin P1 2010), in agreement with those reported in the current study.

However, a randomised trial of 357 patients described no difference in mortality when Hb was maintained between 70 and 90 g/l as opposed to 100 and 120g/l (ref). Therefore, it is possible that accuracy better than within 20g/l is not of actual clinical benefit in the acute setting when haemoglobin is >90g/l, although studies still advocate confirming a BGA result with an EDTA sample prior to definitive management (PC Hebert 2001).

The consistent positive bias reported in the current and previous studies has been proposed to be due to incomplete bottle filling and blood sample clotting before the container is filled. Also, it has been suggested that the sample site may influence intra-subject variation, with differences of up to 8g/l being observed at different sites of capillary measurement (Morris SS 1999).

4.1.4 Lactate

Neither the finger nor ear prick lactate measurements demonstrated sufficient accuracy, as predetermined by our stated aim of 95% of the samples being within 0.5mmol/l of the venous BGA result.

The gold standard method for determining lactate is from an arterial blood gas assessment and this has been the standard for comparison in the majority of reported studies. Previous studies have shown venous lactate to be consistently lower than arterial lactate (Gallagher E.John 1997, Réminiac 2012, Akira Mikami 2013, Ikami A 2013, Talayero Gimenez De Azcarate M. 2013) and a correction of factor of: –0.259 + venous lactate (mmol/L) × 0.996 has been proposed for conversion (Ikami A 2013). Ear pricks can be used to assess oxygenation as the samples are arterialised (Zavorsky 2006) and therefore it is perhaps unsurprising that this modality would provide a negative mean bias compared to the venous sample (i.e. would be more comparable to an arterial sample).

Impact of results on management of acutely unwell adults

Despite the capillary lactate samples not showing sufficient accuracy as compared to our set criteria, there is still potential use for this modality to be used as a screening tool for significant lactic acidosis. The Surviving Sepsis guidelines recommend that a lactate of 4 mmol/l should be considered as a marker of severe sepsis (Dellinger RP 2013). In the current study, capillary sampling was associated with a maximum LOA of -1.2 mmol/l, providing sufficient accuracy to suggest the presence of severe sepsis. However, in the current study, the distribution of results was different between the finger and the ear prick groups. The finger prick showed increasing negative bias with increasing lactate concentrations, suggesting that the finger capillary sample under estimated the lactate more and more, as the lactate level rose. A venous sample may reflect systemic tissue perfusion more than a finger prick, which might be influenced by local perfusion. The ear prick sample did not appear to show the same trend of widening bias, and the bias was more approximated to a normal distribution. This might reflect the arterialisation of the sample.

4.1.5 Patient experience rating and methods of sampling

The pain rating of the different sampling methods varied between the patient and healthy groups, with the healthy participants having lower mean scores for the capillary sample but no significant over all difference when compared to the venepuncture.

The diabetic patient group found both capillary methods significantly less painful than venepuncture and preferred the finger prick blood test. This may reflect prior experience. Finger prick blood testing is commonly used to monitor diabetes by capillary blood glucose metres. A previous study comparing capillary and venepuncture in 70 patients on anticoagulation having INR monitoring regularly showed that the capillary technique was associated with a reduction in pain by 2.6 points on the pain intensity scale. (Gonzalez Diaz E. 2010).

However, it is also possible that some patients had evidence of peripheral neuropathy, a well-known complication of diabetes, which can be associated with reduced pain sensation that starts distally (i.e. at the finger tips and toes) and progresses proximally (Kelsey Juster-Switlyka 2016).

The preference for finger prick sampling over ear prick sampling in the patient group, despite there being no significant difference in levels of pain experienced may also be due to the sampling site. A finger prick blood test occurs at a more distal part of the body. The ear prick blood test involves closer proximity to a patient's face as well as being less familiar method of blood testing. A further problem was that it required more attempts to successfully gain an adequate sample, with 70% of subjects requiring two or more punctures.

The patient group rated a venepuncture as being more painful than capillary sampling. Many patients had undergone multiple blood tests prior to the inclusion of the study, and

many were older, acutely unwell and had limited sites from which to gain a venous sample. Although there are few reported studies of pain associated with serial blood sampling, it is possible that the repetitive sampling from a single site could cause more pain than when a single sample was taken (as was the case in the healthy controls).

Ear prick also sampling requires preparation with transvasin cream for approximately 10 minutes to ensure adequate yield of blood for analysis. This also limits its usefulness given that one of the main reasons of using a POCT test is the rapidly available results.

4.2 How results compare to previous publications

This is the first study to assess the accuracy of capillary glucose results analysed in a blood gas analyser. Previous studies have reviewed accuracy of BGA glucose in venous and arterial samples. The meta-analysis by Inoue in 2013 (Inoue S 2013) included 2 studies where arterial BGA glucose was compared to plasma samples where mean bias results and LOAs were included. They gave mean bias results from - 0.15mmol/l to 0.464mmol/l and 95% LOA ranging from -1.24 to 1.23mmol/l. There were 74 and 171 samples analysed on intensive care unit patients only (Hoedemaekers CW1 2008, Stadlbauer V1 2011, Inoue S 2013).The mean bias (which is slightly positive) is similar to what these 2 previous studies have shown. Three other studies which have reported the mean bias values only (without LOAs) in BGA venous or arterial samples also show positive mean biases of 0.022 (60 samples) (Slater-MacLean L1 2008), 0.1 (84 samples) (Peterson J 2008)and 1.40mmol/l (440 samples) (Corstjens AM1). In the current study, the mean bias was similar to what has been

previously observed for venous BGA. The limits of agreement, however, are wider than the 2 previous studies but do incorporate the same ranges. The reason for this difference is unclear but may due to all the samples in the previous studies being taken in critically ill patient on intensive care units where blood sugars are tightly controlled, and therefore did not cover the wide ranges of samples incorporated in the current study.

The mean biases of 0.26 in the finger prick and 0.46 in the ear prick capillary BGA results are similar to those reported for capillary glucose tested via a POCT glucose in other published studies described in the meta-analysis by Inoue (Inoue S 2013). These showed mean biases ranging from -0.888mmol/l to 0.549mmol/l from 13 studies, with 9 of the 13 studies reporting positive bias results. Limits of agreement were also included in 10 of these studies and the range (upper limit to lower limit) was from 2.44mmol/l to 7.992mmol/l. This is comparable to the range reported in the current study (finger prick; 4.34mmol/l: ear prick, 10.89mmol/l). This meta-analysis described only 1 out of 7 of the studies meeting the IOC criteria (95% of samples within 20% of venous plasma gold standard) with this ranging from 1.4 – 24.8 % of samples and 9.3 % combined (total 2778 samples). In the current study, 10.2% of finger prick samples and 15% of ear prick samples did not meet this criteria. The failure of the BGA samples to show the required level of agreeability within the normoglycaemic range is also similar to what has been reported in previous studies, where 12.5% of mixed venous and arterial samples did not meet the ISO standard (ISO 2013), when compared to venous BGA sample in the current study of 18.7%. This study by Inoue focused predominantly on patients in intensive care. Other studies have reviewed accuracy of blood glucose meters in clinic or outpatient environments, where accuracy has been shown to be

superior. One study reviewed 6 of the commonly used glucose meters in these environments and only 1 failed to meet the ISO standard (from approximately 200 samples for each meter), where 93 % achieved the required level of accuracy (Sujit R. Jangam 2013). There appears to be limited studies assessing accuracy in acutely unwell hospital patients not in critical/intensive care environments.

The current study included analysis with and without an outlying sample where the ear prick BGA glucose value was 0.8mmol/l and the corresponding venous laboratory sample was 19.6mmol/l. This was considered to exceed the variability expected in human physiology and so was assumed to be a procedural or handling error. There were technical issues with sample collection, delaying sample analysis, which could impact upon results. Following this, other samples were collected in close succession or discarded if sampling times exceeded twenty minutes.

For sodium the positive mean bias present across all BGA sampling modalities is concordant with previous studies comparing BGA and laboratory serum values and the limits of agreement shown within the current study are also similar to those recorded previously (Campbell3 200, Anunaya Jain 2009, Binila Chacko 2011, Budak YU1 2012, Quinn LM1 2013) Despite describing similar results, previous studies have disagreed as to whether BGA sodium samples are sufficiently accurate to inform clinical care. The current study however would agree with those studies favouring its use for clinical care when in the normal range as it satisfied the US CLIA guidelines.

The mean bias and LOA for potassium described in the current study are similar to those reported in previous studies, which have compared BGA potassium (taken from arterial samples) to serum samples. Mean biases in these studies ranged from -0.156 to -0.3 with LOAs from -0.72 to -0.4 (lower) to 0.13 to 0.8 (upper) (R King 2000, Anunaya Jain 2009, Binila Chacko 2011, Budak YU1 2012, Quinn LM1 2013). Reported studies provide discordant recommendations as to whether BGA samples can be used to inform clinical care.

Previous studies comparing BGA haemoglobin results have generally used arterial samples but have described similar positive mean bias of up to 0.91 g/l and LOAs (ranging from -11g/l to 14.7g/l) (R King 2000, Ray JG 2002, A Beggs 2006, Quinn LM1 2013).

The only study comparing a capillary BGA lactate to the usual arterial sample was conducted in neonates. Here, a mean bias of -0.08 and LOAs of -0.77 to 0.61mmol/l were reported (Fauchère JC1 2002), which are not dissimilar to the finger prick results of the current study .

4.3 Strengths and Limitations

This study has assessed the comparability of a number of blood parameters, over a wide range of values that you would expect to find in Emergency and acute care. It has used Bland-Altman limits of agreement which enable easy comparison to the standards set by the various associations and IOS and compares the unvalidated method of POCT (capillary

sampling) to methods already in common use (venous BGA sampling). Its setting within the acute medical admissions unit on acutely unwell patients makes it generalizable to a population who may benefit most from this type of blood sampling. It has compared patients experience of the testing methods and used robust statistical analysis to compare the differences in healthy and patient groups as well as across age groups.

There are also limitations to this study. There was a difference in the average age of the healthy cohort compared to the acutely unwell patient cohort. This may impact on test results and could limit the ability to compare results across groups. However, for the majority of parameters, there were no significant differences between the age quintiles, therefore, it is unlikely that age had an influence on the results studied for the majority of the study. There was, however, a statistically significant difference in the bias result for age in potassium although this appears to be due to the influence of the lowest quintile age group only. The cause for this is not clear and there does not appear to be any evidence in the literature which may explain this.

The 3 different sampling modalities were taken sequentially over approximately 20 minutes. The order of sampling alternated throughout the study, to reduce any collection bias. It is possible that variability in the measured results may reflect true physiological changes in parameters over this period. During an acute admission, patients often receive rapid intravenous infusions of therapies that may alter concentrations of blood constituents. The venous BGA and laboratory sample were taken from the same venepuncture sample which

might explain the increased level of agreement noted. This is particularly relevant to glucose where delays of 15 min or more has shown to reduce clinical accuracy to below the ISO standards (Sujit R. Jangam 2013). The effect of the timing of the samples, however, is unlikely to be as significant for sodium or potassium as they do not have the same degree of post-prandial peaks and troughs as glucose and has a more stable diurnal variation (Kamil Fijorek 2013).

An outlying glucose result taken from an ear prick sample has been excluded for some of the analysis (with clear descriptions of where this has occurred). The variation was not thought compatible with physiological change and was instead thought to be due to sampling error. Including this value distorted the plots and did not confer a useful visual representation of the results as it extended the y-axis of the graph to the extent where the other values are not easily distinguishable. Given that ear prick glucose samples did not satisfy the criteria for clinical use even without this outlying sample, the removal of this result from some of the analyses is unlikely to influence any conclusion. However, that such an extreme result occurred would suggest that any results taken following a prolonged sampling time should be viewed with caution and potentially discarded.

This study was conducted unblinded and with no placebo procedure, however all sample analysis was conducted by automated processes, reducing the potential for experimenter bias. Sample bias may impact on this study. Patients were selected following screening of an electronic investigation and prescribing system. All suitable patients were approached in

a sequential order (and not randomly), which could introduce bias. However, the current study includes a broad range of age groups, different ethnicities and a wide range of physiological and pathological blood results, reflecting the type of people that are cared for in the acute medical environment.

Another limitation of this study is that the full range of pathological results were not included. Glucose results included those patients with hyperglycaemic ranges up to levels which may be expected for acutely unwell adults, as hyperglycaemia can be slow to respond to treatment, allowing time to ethically recruit patients without hindering treatment processes. However, patients were not studied in the hypoglycaemic range due to the speed of response of this parameter to correction. As the current study suggests decreased accuracy at lower glucose level, the results cannot be extrapolated to hypoglycaemic levels.

There were only 2 samples with sodium concentrations below 130 mmol/l and no samples within the hypernatraemic range. In light of this, these results should also not be extrapolated to include results beyond the accepted physiological range. With regards to potassium, the current study did not include patients with significantly deranged potassium concentrations either, and therefore results again cannot be extrapolated to comment on hypo or hyperkalaemia. This would be of particular importance as previous studies of arterial samples taken out of the normal range have showed poor agreeability when potassium is less than 3mmol/l and >5mmol/l (R King 2000, Quinn LM1 2013). Despite covering the anaemic range there were no samples where haemoglobin was less than 76 g/l

and only 3 samples less than 90g/l. The LOA did not suggest there was more error at lower or higher haemoglobin concentrations, but the results should not be extrapolated to include results beyond those measured and these should be tested in a further study.

The mean biases for lactate were not normally distributed for the finger prick test. Alternative analysis using regression analysis was adopted and enabled further interpretation for this parameter. The weighted average centiles showed differing results for the 95% confidence intervals compared to the Bland-Altman limits of agreement. This difference was due to the lack of normality of this distribution. The 95% confidence intervals were higher than the corresponding LOA, suggesting less agreeability. This suggests the LOA are likely to be an underestimation of the discordance between the capillary and venous BGA lactate, and interpretation is therefore limited using the Band Altman plots and limits of agreement.

The current results include lactate values of $\leq$5.2mmol/l and given the trend of increasing negative bias with increasing lactate, cannot be extrapolated above this range. However, a lactate of >5mmol/l would be indicative of severe sepsis, suggesting patients with a significant burden of ill health were included in the study. Furthermore, the current study did not compare capillary sampling to the gold standard arterial measurement, although a number of studies report that it is acceptable to use venous lactate as an alternative due to the fairly close agreement (Gallagher E.John 1997, Brad S. Karon 2007, Akira Mikami 2013, Dheeraj Kapoor1 2014).

There were incomplete datasets for some patients. These may include those with poor tissue perfusion and their exclusion may have biased results. However, every attempt was made to include patients who were acutely unwell and as stated, the current study included those who met the definition of severe sepsis.

Most diabetic patients are already familiar with finger prick blood tests and may have complications of the condition which may make this method of blood taking more preferable. This makes these results less generalizable to all patients presenting with acute illness. Some patients were not able to complete a visual analogue scale due to visual difficulties or cognitive impairment. These data were not collected in this patient group and it is unclear whether they might have different perceptions of pain or sampling. Expanding this aspect of the study so as to include a broader range of patients and to increased numbers may help overcome any sample bias.

4.4 Further Work

Further studies could be used to select patients who may fall outside of the ranges included in the current study to ensure these tests are validated for these ranges. This may include selecting patients with anaemia or polycythaemia (as seen in a haematology clinic), and those with significant biochemical disturbances, which are frequently seen in acute kidney injury (potassium) and patients with delirium (sodium).

This was a single centre study using a single model of blood gas analyser (Cobas® b 221). Further study in other centres using other models of BGA should be conducted to ensure these results are generalizable to other centres and when using other machines.

5. Conclusions

This study is the first to assess the accuracy of capillary blood tests measured on a blood gas analyser for glucose, sodium, potassium, haemoglobin and lactate as well as assessing their acceptability for patients.

Finger prick capillary blood tests processed in a blood gas analyser can be used as an alternative to venous testing for the measurement of glucose, in patients who are hyperglycaemic, when glucose is greater than 12mmol/l.

Ear prick testing did not show the same degrees of accuracy or reliability for glucose. There are technical difficulties with this method of testing which may prevent or limits its use. Even with specific training and experience, the assessment often required numerous punctures. It was generally not favoured when compared to the finger prick test in the acutely unwell patients and may not be as acceptable to patients as a method of blood sampling. Due to these problems this method was deemed an inferior method of sampling when compared to finger prick sampling.

Venous BGA sodium and ear prick sodium are sufficiently accurate compared to the US CLIA guidelines and could be used as an alternative to serum testing. These results are generalizable within the normal range, however, further investigation when sodium is less

than 130mmol and in hypernatraemic range needs to be undertaken to confirm the accuracy within these ranges. Capillary BGA Sodium is not sufficiently accurate when taken from a finger prick sample to meet the US CLIA guidelines for accuracy, however the failure of this method by only 0.2% is unlikely to be clinically significant.

Capillary BGA analysis for potassium provides superior accuracy to venous testing, however, does not meet US CLIA standards. It may be used as an alternative to venous BGA testing but intermittent laboratory confirmation should be applied. Given the poor reliability of ear prick testing finger prick methods may be used as the preferred method of capillary BGA sampling.

Haemoglobin measured by both finger prick and ear prick capillary BGA samples are not accurate enough to produce precise haemoglobin monitoring, as defined by the predetermined limits of acceptability. It may be useful to rule out significant anaemia requiring transfusion. Further study is required in the anaemic range when haemoglobin is less than 7g/l.

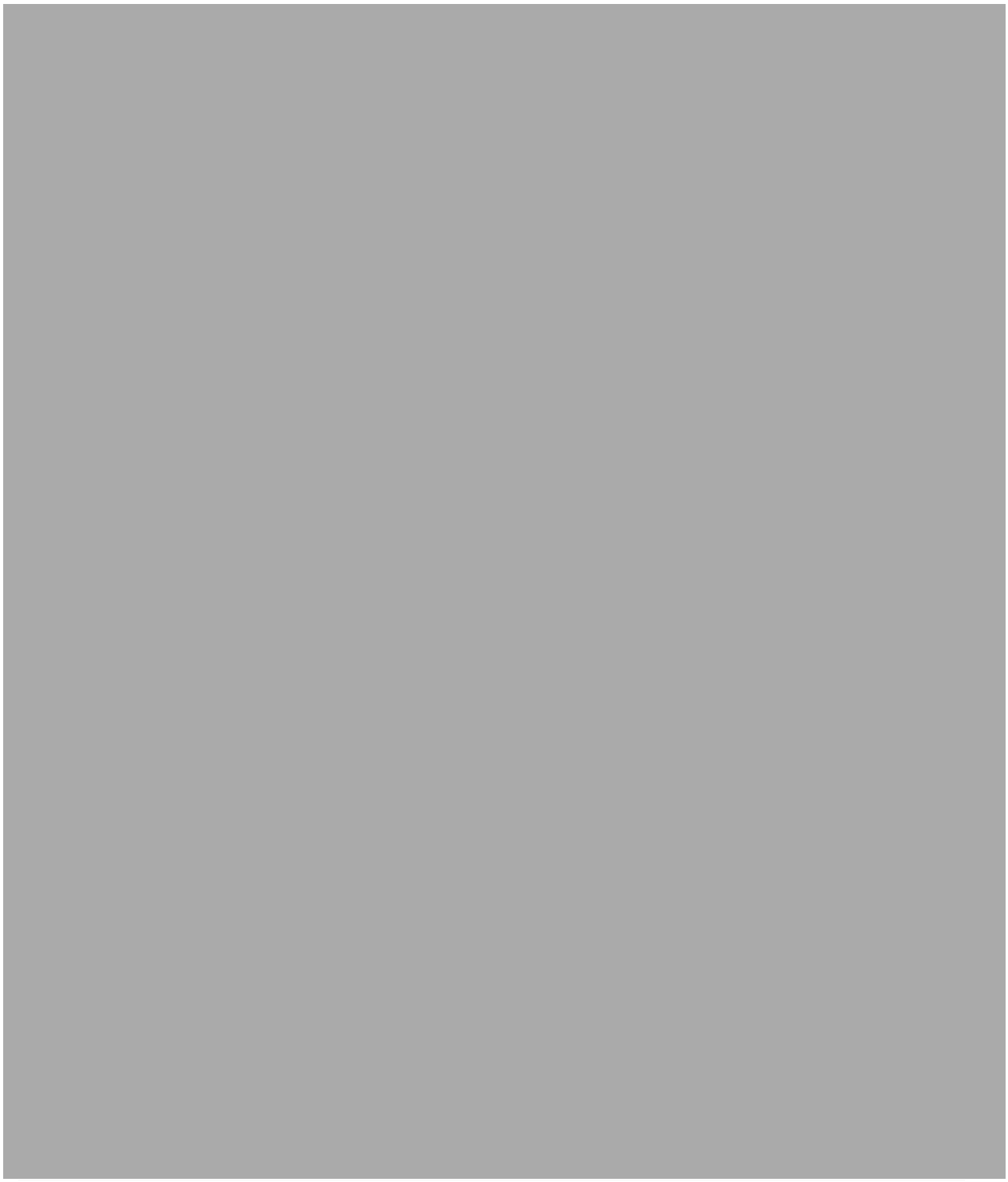
Lactate measured via capillary samples should not be used when precise measurement is required. If precision is not required it may be useful to monitor trends of lactates value but with caution. Further study is required to evaluate its accuracy for values greater than 5mmol/l.

Capillary sampling from the ear and finger prick are less painful as blood taken in the standard way from venepuncture and are a preferred method of blood sampling from acutely unwell diabetic patients.

7. Appendices

Appendix 1. Letter of agreement. National Research Ethics Service Committee - West Midlands (NRES reference 14/WM/1057).

Appendix 2. Letter of agreement. Sponsorship agreed by the University Hospital Birmingham NHS Foundation Trust (UHBFT) Research and Development Committee



Appendix 3. IQC performance data for b221 blood gas analysers in ED and CDU, University Hospital Birmingham NHS Trust

Analyte	ED									CDU								
	QC L1			QCL2			QC L3			QCL1			QCL2			QCL3		
	2SD	CV	Roche	2SD	CV	Roche	2SD	CV	Roche	2SD	CV	Roche	2SD	CV	Roche	2SD	CV	Roche
pH	0.013	0.001	0.05	0.008	0.001	0.006	0.01	0.001	0.007	0.008	0.001	0.05	0.01	0.001	0.006	0.013	0.001	0.007
pO_2	1.14	0.074	6.53	0.883	0.034	5.38	1.081	0.03	4.51	1.565	0.102	6.53	0.808	0.031	5.38	1.136	0.029	4.51
pCO_2	0.210	0.012	2.72	0.183	0.017	1.74	0.112	0.015	2.74	0.331	0.020	2.72	0.248	0.023	1.74	0.110	0.015	2.74
Na	1.33	0.005	0.93	1.28	0.005	0.55	2.11	0.007	0.53	1.33	0.005	0.93	4.12	0.015	0.55	3.06	0.009	0.53
K	0.034	0.006	0.95	0.042	0.004	0.53	0.199	0.014	0.74	0.044	0.007	0.95	0.123	0.013	0.53	0.115	0.008	0.74
Ca^{++}	0.038	0.012	0.98	0.022	0.009	1.20	0.029	0.025	1.43	0.038	0.012	0.98	0.030	0.013	1.20	0.023	0.019	1.43
Cl^-	2.44	0.014	1.96	1.512	0.008	0.97	1.493	0.006	0.87	2.275	0.013	1.96	3.008	0.015	0.97	1.537	0.007	0.87
THb	0.737	0.005		1.514	0.006		4.072	0.011		2.824	0.019		1.514	0.006		9.385	0.025	
Glucose	0.103	0.009	2.38	0.105	0.021	4.83	0.817	0.022	1.91	0.256	0.023	2.38	0.184	0.039	4.83	1.149	0.031	1.91
Lactate	0.290	0.015	4.92	0.067	0.011	4.12	0.067	0.018	7.02	0.283	0.014	4.92	0.135	0.024	4.12	0.100	0.028	7.02

IQC performance data for b221 blood gas analysers in ED and CDU

The data in the column labelled Roche is the expected %CV performance of that analyte using the QC material (between lot number) determined from 2 runs per day with 2 replicates per run for 20 days on 4 different instruments

The 2SD and CV columns are the data obtained for the daily IQC performed on the specified instruments at QEHB during the month of June 2015.**Values of IQC for each parameter**

	L1	L2	L3
pH	7.20	7.45	7.55
pO_2	7.69	13.16	20.41
pCO_2	8.48	5.49	3.674
Na	123	140	160
K	3.0	4.8	7.0
Ca^{++}	1.56	1.18	0.60
Cl^{-}	88	100	118
THb	76	120	180
Glucose	5.7	2.6	18.5
Lactate	10.0	3.0	1.8

Appendix 4. Healthy participant data

					Glucose (mmol/l)				Sodium mmol/l)			
Patient Number	Time taken	Sex	Age	Ethnicity	FP	EP	VBG	VP	FP	EP	VBG	VP
1	17:30	f	42	Caucasian	4.2	4.9	5.2	4.6	141.5	140.9	140.8	142
5	16:30	m	40	Asian	5.1	5.6	5.5	4.8	143.2	142.3	141.7	141
6	13:45	f	49	caucasian	6.2	6.8	5.9	5.3	141.1	140.1	141.1	141
7	15:45	m	26	caucasian	6.4	7.6	7.1	6.1	140	139.7	139.8	140
8	11:50	m	24	caucasion	5.3	5.5	5.1	4.4	143.8	140.9	141.7	141
9	14:15	m	29	caucasian	7.2	9.1	7.9	7	137.7	137.8	139.5	139
10	15:00	f	25	Asian	5.2	5.5	4.8	4.5	140.4	139	140.6	139
11	15:55	f	25	Asian	6.5	6.5	6.1	5.6	142.9	140.5	141.2	139
12	13:55	f	27	caucasian	7.2	7	5.5	4.4	140.7	140.4	141.1	138
13	14:50	f	25	caucasian	7.8		7.6	5.8	141.8	139.6	140.6	139
14	16:15	m	30	Asian	7.1	5.9	5.7		143.5	141.1	142.6	
15	12:50	f	25	caucasian	4.6	5.9	4.3	5.1	141.1	139.3	138.8	138
17	15:30	m	40	Asian	4.4	4.9	4.6	5	142.6	139.9	141.4	139
20	13:20	f	31	Asian (other)	4.8	5.1	4.4	5.1	140.3	138.3	140.6	139
23	11:55	f	42	Asian	4.5	4.4	4.5	5.1	140	138.7	138.6	
25	16:35	m	26	Asian	4.5		4.3	5.2	140.8	ins	142.8	142
28	11:40	f	27	caucasian	4.6	5.3	4.8	4.8	140.8	139.6	139.3	139
39	15:55	m	41	asian	7.2	8.4	7.2	7.7	143.3	143.5	143.6	141
72	11:15	f	49	caucasian	6.7	5.2	6.7	5.6	143	141.5	142.3	141
73	12:30	f	36	caucasian	6.2	6.2	6.1	5	139.1	137.6	138.5	137
74	11:49	f	31	mixed - other	5.1	4.8	5.5	5.3		136.1	137.2	135
2	10:00	f	44	caucasian	5.8	5.4	4.4	4.7	139	134.8	136.9	139
75	12:00	m	35	Asian	5.5	5.4	5.4	5.6		139.8	140.6	138

	Potassium mmol/l				Haemoglobin g/l				Lactate (mmol/l)		
Patient Number	FP	EP	VBG	VP	FP	EP	VBG	VP	FP	EP	VBG
1	3.85	4.02	3.69	4.3	142	137.6	130.8	131			
5	4.19	4.51	3.8	4.3	148.6	152.9	145.7	148	1.2	0.9	1.4
6	4.27	4.18	3.92	4.5	139.9	138.6	136.9	138	1	1.1	1
7	4.14	4.39	3.8	4.5	150.7	160.8	147.2	144	1.2	1.2	1.6
8	3.76	4.09	4.09	4.5	160.6	153.8	151.2	150	1.3	1.3	1.4
9	3.81	4.19	3.58	3.9	151.6	150.7	148.1	146	1.1	0.7	0.9
10	4.27	4.16	4.02	4.6	112.4	102.5	103.1	102	1.1	2.1	1.3
11	3.53	3.77	3.31	3.7	151.4	140.8	137.1	137	1.3	0.8	0.8
12	3.92	3.97	3.68	4.2	148.9	138.7	142	138	1.7	1.1	1
13	4.14	4.44	3.75	4.1	141.8	135.3	135.9	133	1.7	1.4	1.2
14	3.9	4.54	3.82		161.6	157.2	152.1	145	1.3	ins	1.3
15	3.84	3.98	3.72	4.3	138.4	130.1	128.5	123	1.2	0.7	1.2
17	4	3.64	3.55	4	166.35	155	152.6	149	1	0.3	0.8
20	3.76	3.91	3.65	4.3	130.6	128.5	124.1	126	1.4	0.8	1.2
23	3.99	4.03	4.02		139.1	135.1	133	131	1.2	0.9	1.2
25	4.03		3.94	4.3	160.6	157.6	150.7	148	1	0.7	0.9
28	3.89	4.22	3.84	4.3	131.2	134.4	126.2	127	1.2	ins	1.3
39	4.16	4.97	4.24	4.6	149.5	149.9	146.9	144	1.1	0.5	0.6
72	4.11	4.2	4.03	4.3	137.5	135.3	135	139	1.3	1.4	1.1
73	3.65	3.6	3.54	3.9	133.8	127.9	132.7	135	1.6	0.7	1.6
74	4.23	3.97	3.87	4.3	141.7	132.8	131.9	130	1.3	0.9	1.4
2	4.48	4.92	4.31	4.8	142.3		135.1	134	0.8	0.6	0.9
75	4.36	4.35	4.26	4.7	139.6	145.9	136.3	132	0.7	0.6	0.7

Appendix 5. Patient Data – Patients with Glucose 10-15 mmol/l

					Glucose (mmol/l)				Sodium mmol/l)			
Patient Number	Sex	Age	Ethnicity	Admitting Diagnosis	FP	EP	VBG	VP	FP	EP	VBG	VP
16	f	84	asian	CAP + NSTEMI	13.8	12.6	13.3	13.5	137.5	137	136.5	138
19	f	69	afro-caribbean	Vomiting	14.2	13	13.7	12.7	138.8		138.3	138
30	m	61	caucasian	infective exacerbation of bronchiectaisis	7.7	8.7	8.1	7.6	137.6		136.8	137
31	m	78	caucasian	exacerbation of COPD	13.8	13.3	13.1	13	138.3	136.8	137.3	136
32	f	38	caucasian	collapse	11.6	13.1	11.4	11.5	134.8	134.6	133.8	132
35	f	73	asian	Constipation/obstruction	11.3	12.2	11.6	11	137.7	138.8	137.8	137
36	m	58	asian	Gastroenteritis	9.5	10.7	9.7	9.3	137.8	137.8	137.7	136
37	m	37	asian	CAP	6.2	8	8.5	8.7	136.8	135.6	135.7	133
41	m	65	caucasian	urosepsis/dka	11.2	11.8	11.7	11.5	134.8	132.6	133	131
42	f	51	caucasian	Hyperglycaemia, renal colic	15.5	16.4	15.6	15	140.2	139.6	139.3	137
43	f	72	caucasian	chest pain	13.1	13.5	13.2	12.4	137.6	142.7	139.6	139
45	f	80	caucasian	Fast AF, LVF sepsis	12		12.1		137.3		137.5	136
46	m	74	caucasian	sepsis	10.7	12.1	11.1	11.1	135.8	136.8	135.4	137
47	f	83	asian	aki, hypercalcaemia	14.5	15	13.7	13.9	137	136.7	135.2	134
48	m	63	caucasian	collapse	12.8		13	11.6	131.2		132.1	130
50	f	55	caucasian	fever/sepsis	14.6	14.8	14.5	13.3	138.1	137.1	138.6	137
54	m	47	afro-caribbean	Infected foot ulcer	12.6		12.8	13.1	141.1	141.4	140.3	140
55	m	75	asian	Risperidone overdose	9.7	11.9	10.5	10.5	139.6	137.7	138.5	137
56	f	55	afro-caribbean	Hyperglycaemia	6.5		6.5	6.1	144		142.5	143
57	f	83	caucasian	hypoglycaemia	13.5	13.7	13.6	12.8	134.4	133.8	132.9	133
63	m	82	caucasian	infective exacerbation of COPD	19.4	20.1	19.2	18.2	132.1	131.8	133	134
66	m	48	caucasian	confusion	14.4	14.1	14.1	13.6	121.6	122.6	121.4	118
68	f	79	caucasian	sepsis	15.7		16.3	16.1	136.1	136.3	134.8	135
70	m	87	afro-caribbean	sepsis	11.3	11.6	10.3	9.9	143	141.7	142	142
71	m	79	caucasian	exacerbation of COPD	29	29.9	28.3	28.2	137.9	137.9	136.6	137

	Potassium mmol/l				Haemoglobin g/l				Lactate (mmol/l)		
Patient Number	FP	EP	VBG	VP	FP	EP	VBG	VP	FP	EP	VBG
16	4.03	4.09	3.66	4.2	132.9	123	116.3	111	2	1.6	1.7
19	3.55		3.41	3.7	124.8	119.2	118	119	1.8	1.7	1.7
30	3.77		4.02	4.3	104.1	104.2	106.5	104	1.8	1.7	1.8
31	5.06	5.53	4.95	5.1	157.7	156.6	151.2	152	2.1	1.9	2.2
32	3.98	4.08	4.04	4.6	141.7	141.5	136.6	136	0.8	1	0.9
35	4.8	5.42	4.79	5.1	130.4	134	120.9	117	1.6	1.8	1.6
36	4.03	4.19	3.81	4.2	120.3	125.3	119.5	117	1.5	1.5	1.6
37	4.2	3.8	3.79	4.3	126.8	143.1	122	121	1.9	2.2	2.6
41	3.83	4.33	3.42	3.8	122.3	130.8	128.5	125	1.9	2.2	1.8
42	3.56	3.71	3.29	3.5	129.6	117.3	117.4	117	1.4	1.2	1.4
43	4.62	5.02	4.67	4.9	115.9	121.6	113.8	115	2.4	2.2	2.1
45	3.83		3.64	4.3	118.1		112.5	110	1.4		1.4
46	4.25	4.22	4.07	4.3	98.5	98.4	93.1	92	2	2	2
47	5.41	5.74	5.48	5.7	105.8	105.2	93.6	93	1.2	0.9	0.9
48	3.61		3.47	3.7	146.5		136.3	134	1.7		1.7
50	3.57	3.72	3.59	4.6	145	143.7	137.2	137	1.6	0.6	2.4
54	4.36	4.84	4.15	4.6	121.8	102.5	111.7	107	0.8		0.7
55	4.24	4.92	3.82	4.2	116.2		115.3	113	1	1.4	0.9
56	3.66		3.58	4	114		112.9	111	1		1
57	4.56	4.63	4.3	5	121.6	113.1	107.7	104	0.6	0.6	0.5
63	4.11	4.56	3.87	4.3	136.1		127.5	117	4.1	5.2	4.7
66	4.31	4.19	3.98	4.3	137.2	128.5	125.9	126	0.7	0.4	0.7
68	4.05	4.77	3.58	4	116.4	123.5	107.6	101	1.9		1.9
70	4.62	4.26	3.97	4.7	139.8	129.9	125.5	123	4.2	1.9	2.9
71	4.73	5.6	4.4	4.7	136.8		137.7	136	4	4	4.2

Appendix 6. Patient Data – Patients with Glucose >15 mmol/l

					Glucose (mmol/l)				Sodium mmol/l)			
Patient Number	Sex	Age	Ethnicity	Admitting Diagnosis	FP	EP	VBG	VP	FP	EP	VBG	VP
18	m	19	caucasian	Hyperglycaemia	25.5	24.4	24.3	23.4	138.2	136.1	136.2	135
21	f	54	caucasian	insulin od	28.6	27	27	28.2	134	135.6	135.2	133
22	m	80	caucasian	Chest pain	25.2	27	25.2	27.2	134.4	132.2	133.4	131
24	m	71	caucasian	CAP	21		21.2	21.6	139.5	140.7	141.9	140
26	m	62	asian	LVF	14.1	15.2	12.9	13.3	132.8	133.8	132.9	134
29	m	52	asian	Chest pain	34.4		35.6	39	128.2	128.5	128.5	125
33	m	57	caucasian	infected ulcer/cellulitis	16.5	16.6	16.2	15.9	132.5	132.7	132.8	132
34	f	83	caucasian	sepsis/delirium	20.4	20.9	20.9	21	139.1	140	139	137
38	f	53	caucasian	sepsis/cellulitis	16.7	17.4	17	16.6	132.1	133	132.2	132
40	f	65	caucasian	Anaemia	21.5	22.6	21.5	20.9	138.9	137.5	138.9	137
44	m	84	caucasian	Fall-multifactorial	13.6	14.3	13.9	13.7	140.2	138.9	139.6	138
49	m	56	caucasian	fall	20.9	21.6	21.3	21.5	135.1	133.8	134.6	138
51	f	83	caucasian	fall	14.2	15	13.5	14.4	134.4	134.6	134.1	132
52	m	78	afro-caribbean	burns, aki	18		17.5	17.1	134		133.9	132
53	m	57	afro-caribbean	urinary sepsis	18.9	0.8	18.5	19.9	141.2	139.9	139.5	139
58	f	74	asian	Hyperglycaemia , AKI	6.8	8.3	6.1	5.6	133.9		133.2	134
59	m	66	caucasian	DKA	17.3	15.7	19.1	19	147.3	142.6	144.7	143
60	f	74	caucasian	CAP	24.8	24.4	24.2	23.9	136.2	135.8	135.5	136
61	f	63	caucasian	sepsis ?source	19	21.2	19.5	17.8	137.7	136.9	136.7	138
62	m	33	caucasian	Infective exac COPD	21.7	22.1	21.4	19.7	140.2	143	141.7	137
64	m	83	caucasian	vacent episode	21.7	21.6	22.6	20.3	136.6	137.8	136.7	137
67	m	82	afro-caribbean	hypoglycaemia	20.3	19.6	20.2	19.6	134.4	134.9	133.7	134
69	f	71	caucasian	?CCF	18.3	19.7	18.7	18	134.4	133.4	133.3	133

	Potassium mmol/l				Haemoglobin g/l				Lactate (mmol/l)		
Patient Number	FP	EP	VBG	VP	FP	EP	VBG	VP	FP	EP	VBG
18	4.42	4.44	4.08	4.4	137.9	138.1	132.9	132	2.9	2.8	2.8
21	4.65	5.23	4.55	4.8	136.3	138.8	126.3	127	2.6	2.6	2.1
22	4.92	4.81	4.72	5	117.5	127.1	119.3	119	0.9	0.9	0.9
24	5.4	5.82	4.47	4.9	172.6	172.6	165	163	5.4	ins	5.8
26	3.34	3.95	3.36	3.7	127.1	132.6	122.3	126	2.2	2.5	3.1
29	4.17	4.27	3.99	4.4	159	140.7	145.6	146	1.6	2.3	1.6
33	4.56	4.83	4.46	5.1	124.8	118.8	113.5	113	1.4	1.3	1.5
34	3.45	3.68	3.58	4.1	142.4	128.4	136.1	130	4	5	5
38	4.19	4.35	3.98	4.3	81.6	83.5	74.5	74	2.7	2.6	2.6
40	4.9	4.38	4.9	4.7	82.3	75.9	82.3	76	2.4	2.1	2.4
44	4.11	4.48	3.94	4.2	101.9	93.4	98.4	96	1.2	1.3	1.4
49	4	4.78	3.77	4.1	157	150.1	147.3	149	0.5	0.6	0.6
51	4.02	4.08	3.9	4.2	97.5	97.4	93.1	92	2.3	2.2	2.2
52	4.3		3.62	4	123.4		121.2	119	1.6		1.2
53	4.78	5.08	4.26	4.7	157.1	145.6	133	129	0.7	0.6	0.6
58	4.94		4.43	5.1	103.2		99.2	110	2.4	2.8	2.7
59	4.71	3.57	3.72	4.2		94.9	83.2	84	4.4	3.1	4.4
60	4.45	4.55	4.13	4.5	138.1	140.3	132.9	128	2.5	2.1	2.4
61	3.75	3.9	4.37	4	122.5	129.8	114.8		2.6	2.7	2.9
62	4.24	4.25	4.72	4.6	137.8	139.9	146.7	136	1.9	1.7	2.2
64	4.28	4.33	4.02	4.4	128.5	128.6	119.7	121	1.7	1.7	1.9
67	4.77	4.7	4.52	4.8	93.9	97.3	92.7	89	1.6	1.4	1.5
69	3.71	3.77	3.37	3.7	134.4		126.7	118	2.1	2	1.8

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