THE ASSOCIATION BETWEEN PREOPERATIVE FASTING TIME, BLOOD GLUCOSE CONCENTRATION AND BLOOD KETONE LEVELS IN PEDIATRIC PATIENTS UNDERGOING SURGICAL PROCEDURES AT THE KENYATTA NATIONAL HOSPITAL

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STUDENT'S DECLARATION

I herein declare that this dissertation is my original work and has never been submitted in any form or manner to a university for award of degree.

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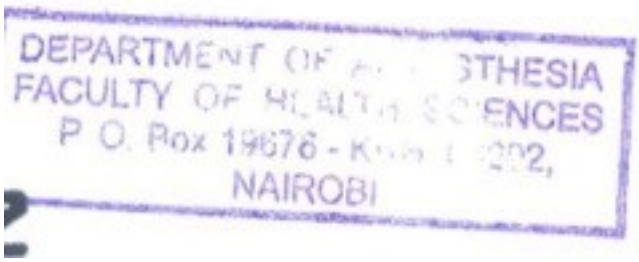

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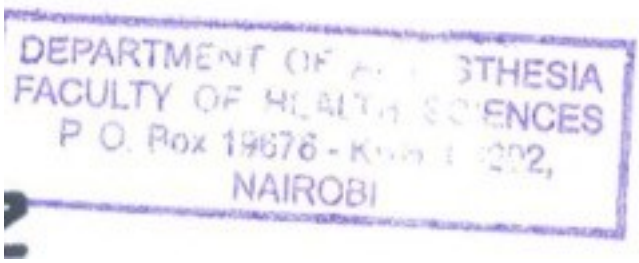

CERTIFICATE OF AUTHENTICITY

This is to certify that the dissertation is an original work of the author and has been duly reviewed and approved for submission to the KNH/UoN-ERC. The research was carried out at the main and satellite theatre areas of the Kenyatta National Hospital.

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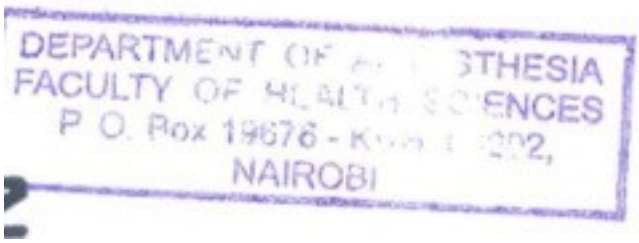

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ABBREVIATIONS

ADA	American Diabetes Association
ASA	American Society of Anesthesiologists
ATP	Adenosine triphosphate
B-OHB	Beta-hydroxybutyrate
CDC	Centre for Disease Control and Prevention
CO2	Carbon dioxide
DKA	Diabetic Ketoacidosis
ENT	Ear Nose Throat
ESAIC	European Society of Anesthesiology and Intensive Care
GLUT	Glucose Transporter
H2O	Water
KNH	Kenyatta National Hospital
mmol/L	millimoles per litre
NPO	nil per os
PKA	Protein Kinase A
POC	Point of Care
RBS	Random blood sugar
RCT	Randomized Control Trial
WHO	World Health Organization

DEFINITION OF KEY TERMS

Anaesthesia Care Provider:	A physician, resident, clinical officer or nurse qualified or in training providing anesthesia/critical care for patients.
Dysglycaemia:	Blood glucose levels above or below the thresholds defining hyper/hypoglycaemia
Hyperglycaemia:	Capillary or venous blood glucose above 6.0 mmol/L
Hyperketonemia:	Blood ketone level above 1.0 mmol/L
Hypoglycaemia:	Capillary or venous blood glucose below 4.0 mmol/L
Ketoacidosis:	Blood ketone measurement 3.0 mmol/L or higher
Ketonemia:	Blood ketone level above 0.6 mmol/L
Paediatric age group:	All paediatric patients zero to thirteen years of age

ABSTRACT

Background/Introduction: Preoperative fasting guidelines have been updated to ensure the risk of paediatric patients developing hypoglycaemia, ketoacidosis, and derangement in acid-base balance during the preoperative fasting period is reduced since they are unable to properly regulate glucose metabolism due to their anatomical and physiologic differences when compared to adults. However, challenges at resource limited, high-volume centers such as the Kenyatta National Hospital (KNH), have led to inefficient implementation of the preoperative fasting recommendations.

Objective: to determine the association between preoperative fasting time, blood glucose concentration and blood ketone levels in pediatric patients undergoing surgical procedures at the National Hospital.

Methods: an analytical cross-sectional study conducted at the Kenyatta National Hospital main theatres, the ophthalmology and ENT satellite theatres involving two hundred and twenty-two (222) paediatric patients aged 0-13 years who met the inclusion criteria. Consenting paediatric patients were recruited on the eve and day of surgery and blood samples of 0.5 microlitre collected from the fingertip or heel at induction of anaesthesia. Blood glucose and ketone levels were measured using POC handheld Abbott Freestyle Optimum Neo combined glucose and ketone meter. Statistical analyses were performed using SPSS version 26 and Pearson's correlation was used to determine the strength and direction of the associations with statistical significance tested at 5% (p-value ≤ 0.05).

Results: The overall median fasting time was 11.0 (IQR 7-14) hours with 218 (98.2%) deviating from the preoperative fasting guidelines. There was hypoglycaemia in 65 (29.3%) patients and high ketone levels in 92 (41.4%) of the patients. The study found poor correlation between preoperative fasting time and blood glucose level which was statistically significant ($r = -0.190$, $p = 0.04$) and a poor correlation between preoperative fasting time and blood ketone levels which was not statistically significant ($r = -0.086$, $p = 0.202$). There was also poor association between age, weight gender and types of last meal and the glucose level at induction of anaesthesia.

Conclusion: there was prolonged preoperative fasting time and marked deviation from current documented preoperative fasting guidelines among paediatric patients at the Kenyatta National Hospital. The correlation between preoperative fasting time and blood glucose concentration and blood ketone levels was not strong however it is clinically significant as it impacts perioperative outcomes.

1.0 CHAPTER ONE: INTRODUCTION

1.1 Background Information

Preoperative fasting guidelines have been updated in the last few years with the goal of addressing several concerns in the pediatric age groups. While the historical basis for preoperative fasting has been more focused on preventing and reducing the risk of bronchopulmonary aspiration of gastric contents during induction of anaesthesia, other complications including those related to metabolic and haemodynamic changes still have serious impact on the outcomes of patients during the perioperative period. The risk of hypoglycemia, ketoacidosis, and derangement in acid-base balance as a result of preoperative fasting in children is believed to result from the inability of pediatric patients to properly regulate glucose metabolism. Unlike normal healthy adults who maintain blood glucose levels during fasting by the reduction in insulin secretion and an increase in glucose regulatory hormones including growth hormone, glucagon, cortisol and epinephrine, pediatric patients have far less liver and muscle glycogen stores compare to adults, coupled with a higher metabolic rate resulting into hypoglycemia and ketosis at a faster rate.[1,2]

Regardless of the low liver and muscle glycogen stores in children, most studies have found varying and conflicting results on the actual effects of preoperative fasting on blood glucose in these children. Hussein Endris Assen et al found that 26.2% of pediatric patients undergoing elective surgical procedure were hypoglycemic on induction of anaesthesia following a cross sectional study in a teaching hospital in Addis Ababa in 2021 involving 258 children undergoing elective surgical procedures.[3]

A study done by Haymond et al in 1982 on the differences in gluconeogenic substrates during short-term fasting in men, women and children also found children with the lowest blood glucose reading and highest beta-hydroxybutyrate concentration compared to adult males and females. The study found an inverse relationship between blood glucose and ketones (beta-hydroxybutyrate) throughout the fasting period in all three groups.[4]

Hajian P. et al, on the other hand, found no significant effect of the duration of fasting on blood glucose in children when they did a cross-sectional study involving 50 children between the ages of 3 to 12 years in a Hospital in India in 2020.[5] Although the duration of fasting was within a 12 hour period, they however found a significant negative correlation between the duration of fasting with liquids and systolic blood pressure drop. Numerous other studies also did not find statistically significant correlation between the duration of fasting

and plasma glucose. However, most concluded that fasting within a 12-14 hours period may not influence the blood glucose to a large extent in older children but may have serious consequences on other parameters including metabolic substrates and haemodynamics. In fact, normal or near normal blood glucose measurement did not rule out significant blood ketone levels and significant risk of acidosis in these fasting pediatric patients. In the RCT done by J.M. Saudubray et al. looking at the variation in plasma ketone bodies during a twenty-four-hour fasting between in normal and hypoglycaemic children ages 4 months to years, they found a highly negative correlation between blood ketone bodies and blood glucose, especially for ketones corresponding to glucose levels between 2.5 and 3.6 mmol/L[6].

At the Kenyatta National Hospital, patients scheduled to undergo surgery are fasted using guidelines from the American Association of Anesthesiologists (ASA) and the European Society of Anaesthesiology and Intensive Care (ESAIC) and other recent recommendations. Based on recent research done in children at KNH by Mokaya in 2017 on the intra-operative glycaemic dynamics of children undergoing elective surgery under general anaesthesia, a median fasting time of 9.7 hours with incidence of hypoglycaemia in 15.2% of the patients was found.[7]

These results show similar findings from other studies demonstrating longer fasting time and hypoglycaemia in pediatric patients. Prolonged fasting, starvation, organic academia, glycogen storage disease and deficiencies in gluconeogenic enzymes are some of the common causes of non-diabetic ketoacidosis in children.[8]

Ketoacidosis from non-diabetic causes is becoming a frequent occurrence in clinical practice with severe morbidity and mortality as those with diabetes despite the ketones being an alternative source of energy during prolonged fasting in pediatric patients. In a case series between 2018 and 2020, Elsayed et al conducted a prospective collection of cases in which they found 11 of the patients from 5 months to 5 years with ketoacidosis were from non-diabetic causes presenting with dehydration, hypoglycemia, and convulsions.[9]

Ke Bai et al. also reported 5 pediatric patients with non-diabetic ketoacidosis presenting with dehydration, poor appetite, and Kussmaul breathing in a retrospective case between 2009 and 2015.[10] These patients were noted to have a faster recovery from acidosis when treated with insulin and glucose than those treated with bicarbonate.

In the study done by K.J.B. Lamers et al. on the concentration of blood components related to fuel metabolism during prolonged fasting in children in 1985, there was a clear negative relationship between age and ketone levels with increased ketogenesis in younger children compared to older ones while higher levels of ketones with diminished glucose were also

seen with prolonged duration of fasting.[11] Similar findings were demonstrated in another study done by K.J.B. Lamers et al. involving 72 children ages 3 to 15 years where the interrelationship between blood components involved in metabolism, sex, age and glucose was studied after an overnight fast of about 14 hours.[12] The study found blood ketones and non-esterified fatty acids were increased in younger children compared to older ones after overnight fast while also having a negative correlation with blood glucose levels during the same fasting period. The study suggested that after overnight fasting, lipolysis and ketogenesis are more active in younger children than older ones due to inadequate gluconeogenic pathways.

Thus, assessment of blood ketone levels in fasted pediatric patients in addition to glucose monitoring could ensure better perioperative safety, treatment options and outcomes in high-risk groups.

2.0 CHAPTER TWO: LITERATURE REVIEW

2.1 The Physiology of Glucose Metabolism

Regardless of the intake of carbohydrates, proteins or lipid-based meals, glucose is the ultimate product which serves as the major fuel source for metabolic processes for the growing human body However, glucose absorption from the intestine, its uptake and release by the liver, its uptake by peripheral tissues, and other factors, such as fed or fasted status, all affect how much glucose is typically present in circulation. Glucose metabolism and the maintenance of glycaemic control is thus under a tight regulation of pathways of glycogen synthesis, glycogenolysis and gluconeogenesis ensuring a range between 4 and 6 mmol/L, with variable rise and fall during the postprandial and fasting periods which does not normally fall below 3.5 mmol/L during normal fasting.[13]

This is due to a dynamic balance between insulin and glucagon, amongst many other hormones and factors, which keeps a dynamic equilibrium with a regular and constant supply of glucose to tissues and cells while maintaining this narrow range of blood glucose during the fed and fasting state. The quantity and duration of action of each of these hormones will depend on the factors associated with the fed and fasting states of each individual patient.[14]

2.1.1 Glucose Metabolism in the Fed State

Following the intake of meal, glucose is liberated through hydrolysis and absorbed into the blood. Insulin, a polypeptide hormone, is the main regulator of glucose uptake during the fed state. The release of insulin from the beta cells of the pancreas is primarily stimulated by glucose level in the blood, although neural, metabolic and endocrine stimuli also play vital roles. Glucose-induced insulin secretion from the beta cells of the pancreas is usually biphasic, having an initial rapid surge from stored insulin, followed by delayed slow rise over 15-20 minutes from newly synthesized hormone.[15]

This glucose-induced insulin release happens via physiologic mechanisms involving several steps. Glucose available in blood during the fed state enters beta cells of the pancreas via glucose transporter (GLUT-2), a membrane-bound sodium-independent glucose transporter thereby initiating glucose transport. Inside the cytosol of these pancreatic beta cells, glucose is then phosphorylated to glucose-6-phosphate by glucokinase, a type of hexokinase with lower affinity for glucose, leading to “glucose sensing” over its physiologic range. Following phosphorylation, glucose then enters the glycolytic pathway within the cytoplasm where pyruvate is produced, then metabolized within the mitochondria of the beta cells into carbon

dioxide (CO2) and water (H2O) via the citric acid cycle with the formation of Adenosine triphosphate (ATP) by oxidative phosphorylation.

The increased amount of ATP and NADH, both of which are secretory signals, initiates the closure of ATP-sensitive potassium channels and K+ efflux resulting into depolarization of the beta cell membranes with opening of the voltage-sensitive calcium channels, influx of large quantity of extracellular calcium ions leading to the exocytotic release of insulin granules from the readily releasable pool.[16]

The insulin released from these granules is responsible for the initial rapid surge after meal. A sustained release of insulin will depend on the continuous stimulation of the beta cells by glucose. It should also be noted that substrates other than glucose, including leucine, keto-isocaproate, and methyl succinate can also initiate insulin secretion. Other agents, called potentiators of insulin secretion, have the ability to 'amplify' the effect of glucose on the β cell and include some fatty acids, the amino acid arginine, and the incretin hormones.[8, 9, 10]

The surge in insulin release inhibits glucose production from hepatic cells through the inhibition of hepatic phosphorylase while stimulating glucose uptake into muscle and adipose tissues in addition to hepatic uptake. This uptake and release of glucose from muscles, adipose, and other tissues is based on the expression of various glucose transporters on cell surfaces during the fed and fasted state. One of the main glucose transporters is the GLUT4 which can be found primarily in skeletal muscle, cardiac muscle, adipose and brain tissues.

Normally located in cytoplasmic vesicles in their inactive form, GLUT4 become activated via glucose-stimulated insulin release leading to their expression on the cell membranes of these muscles and adipose tissues. It is stated that about 50% of the glucose taken up by muscles is oxidized while up to 35% is stored as glycogen and another 15% released as lactate and alanine.[17]

Insulin also activates liver glucokinase, promoting the phosphorylation and entrapment of glucose inside the liver cells for conversion to glycogen with glycogen synthase being responsible for polymerizing monosaccharide into glycogen molecules. This process is at its highest during the first 30 minutes after a meal when the gradient of glucose via the portal-arterial system is at its maximum, thus ensuring more movement of glucose through the liver. The amount of glycogen to be synthesized in the liver is dependent on the extent of glycogen stores, a capacity that is limited in the pediatric age groups especially the younger children. About 17% of the oral glucose intake is used for hepatic glycogen synthesis via direct and indirect pathways and conversion to other high energy stores including triglycerides.[6, 8]

All extra glucose that enters the liver cells is converted to fatty acids. The liver produces triglycerides from the produced fatty acids, which are then delivered into the blood as lipoproteins. Because there are fewer precursors available due to insulin's decreased amino acid release from muscle and other extra-hepatic tissues, gluconeogenesis is inhibited.

2.1.2 Glucose Metabolism in the Fasting State

When a patient has stopped the intake of food and water during preoperative fasting, the body still maintains blood glucose within the physiologic limits. This is due to the actions of glucagon and other counter-regulatory hormones and chemical mediators to harness stored glucose in the form of glycogen or its production from precursors. During fasting the level of insulin falls as available blood glucose level drops while glucagon, growth hormone and catecholamine levels increase significantly. Glucagon, a 29 amino acid peptide hormone, is released from the α-cells of the pancreas mainly in response to insulin induced hypoglycemia. This hormone has biding sites in several tissues including the liver, brain, intestine, pancreas, kidneys, and adipose tissues.

Its primary role is to stimulate hepatic glucose production through various mechanisms which include glycogenolysis and gluconeogenesis while at the same time inhibiting glycogenesis and glycolysis. In fact, parenteral and intra-nasal glucagon has been used to treat severe hypoglycemia especially in patients with diabetes on insulin therapy.[18]

The activation and release of glucagon from the pancreatic cells is said to be in a pulsatile fashion which then binds to glucagon receptors, G-protein coupled receptors, on hepatic cell surfaces. When glucagon binds to these surface receptors, there are conformational changes and multiple enzymatic steps leading to the activation of protein kinase A (PKA), a process that also results in an enhanced release of glucagon.[19]

The activation of PKA allows glucagon to control hepatic glucose output via modifications in glycogenolysis, glycogenesis, gluconeogenesis and glycolysis which it does by activating glycogen phosphorylase kinase. The activated glycogen phosphorylase kinase leads to phosphorylation of glycogen through glycogen phosphorylase resulting in increased glycogenolysis and the production of glucose-6-phosphate with further breakdown into glucose by glucose-6-phosphatase and subsequent increase in hepatic glucose output to the blood.[20] Glucagon also directly stimulates the activities of glucose-6-phosphatase leading to increased breakdown of glucose-6-phosphate into glucose. In addition to its stimulatory effects of glycogenolysis, glucagon also inhibits glycogenesis. This inhibition ensures that the pool of hepatic glucose is additionally increased. Hepatic glycogenolysis is said to maintain

glucose levels during the fasting state in the initial stages but due to the limited amount of stored glycogen, hepatic gluconeogenesis from glycerol, lactate and amino acids usually increases after about 8 hours or more of fasting.[21]

With increasing hours of fasting, there is a decrease in glycogenolysis with subsequent increase in gluconeogenesis. It is estimated that 54% of glucose is derived from gluconeogenesis after about 14 hours of fasting, rising to about 64% after 22 hours and around 84% by 42 hours.[22] Although the liver is the primary organ for gluconeogenesis, the kidneys also contribute to endogenous glucose production during prolonged hours of fasting with an estimated 40% of total gluconeogenesis during such periods.[23]

Glucagon potentiates gluconeogenesis by activating gluconeogenic enzymes and by increasing the uptake of gluconeogenic amino acids. These gluconeogenic substrates, including pyruvate, lactate, glycerol and amino acids, are either generated in hepatic cells or transported to the liver via circulating substrates from extra-hepatic tissues. There are four enzymes considered very important and unique to gluconeogenesis and can be directly or indirectly activated and enhanced by glucagon during fasting. These enzymes include pyruvate carboxylase, phosphoenolpyruvate carboxykinase (PEPCK), fructose 1,6-biphosphatase, and glucose 6-phosphatase. Since gluconeogenesis is considered essentially a reversal of glycolysis, bypassing the highly exergonic and irreversible steps of glycolysis requires the four enzymes, a process largely occurring in the liver with the renal cortex involvement to a lesser extent.[24]

During conditions of low or limited oxygen such as during vigorous exercise or low perfusion states, cells perform anaerobic glycolysis for ATP production. This is seen mostly in muscle and red blood cells where lactate is produced through anaerobic glycolysis, gets shunted to the liver and become oxidized to pyruvate before being converted to glucose through gluconeogenesis using the Cori cycle.[25,26]

In addition, certain gluconeogenic amino acids such as leucine, isoleucine, phenylalanine, thyrosine and tryptophan become transaminated into various intermediates to enter the gluconeogenic pathway. These listed amino acids are mostly ketogenic in addition to fatty acids. Others such as methionine, histidine, and valine are also important precursors of gluconeogenesis.

Regardless of the precursors, gluconeogenesis is a complex metabolic process that takes place within the cytosol and mitochondria of hepatic cells and to lesser extent, cells in the renal cortex, with the main purpose of maintaining blood glucose during fasting. [8,22,27]

2.1.3 Ketone Metabolism

Ketogenesis is a pathway through which ketone bodies are produced as alternative energy source. Small amounts of ketones are usually being produced continuously in normal healthy individuals but gradually increase during the fasting hours where there is a condition of decreased carbohydrates or increased fatty acids.[28]

With insulin level reducing during the fasting period, glucagon and other counter regulatory hormones trigger increased lipolysis with glycerol and fatty acids being liberated. Glycerol is converted to glucose via gluconeogenesis unlike fatty acids which are usually not. Ketogenesis occurs in the mitochondria of hepatic cells where fatty acids are transported using the carnitine shuttle enzyme and become cleaved through beta-oxidation into acetyl CoA. Multiple enzymatic steps lead to the production of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) by HMG-CoA synthase. The next step is the enzymatic conversion of HMG-CoA by HMG-CoA lyase into acetoacetate which can then be cleaved either through non-enzymatic decarboxylation into acetone or via the action of beta-hydroxybutyrate dehydrogenase into beta-hydroxybutyrate. It should be noted that of the three ketone bodies, acetoacetate and beta-hydroxybutyrate are the ones used as alternative fuels by mostly muscle and brain cells during low insulin states.

Outside the liver, beta-hydroxybutyrate is converted back to acetoacetate which can then be converted to acetyl CoA before its entry into the citric acid cycle and the subsequent production of multiple ATP molecules from each of the Acetyl CoA through oxidative phosphorylation. Acetone on the other hand is not converted back to acetyl CoA and can therefore be excreted through urine or exhaled via the airways. While low carbohydrate availability and increased fatty acids levels lead to increased ketone production, the main regulation of ketogenesis is through insulin.

Low insulin level triggers ketogenesis but is usually enhanced by glucagon and other counter regulatory hormones including catecholamines, cortisol and thyroid hormone by their actions to increase lipolysis thus making free fatty acids readily available. Although fatty acids are the main precursors for the production of these ketone bodies, certain amino acids including isoleucine, leucine, tyrosine, tryptophan and phenylalanine, can also be used for ketogenesis.[8,29,30]

There is a reciprocal relationship between fat and carbohydrate breakdown, with the oxidation of fatty acids being inhibitory to glucose uptake by insulin-sensitive tissues thereby enhancing hepatic glucose output. The muscles and other tissues which are major users of

glucose as their primary energy source during the fed state usually switch to fatty acids and ketones during the fasting state with low insulin levels since these tissues depend on insulin for glucose uptake. These ketone bodies, acetone, acetoacetate and beta-hydroxybutyrate, are water soluble and thus do not need lipoprotein for their transport. Acetoacetate and beta-hydroxybutyrate are however acidic with pKa of 3.6 and 4.7 respectively. This means during conditions of enhanced ketogenesis such as in patients with diabetes, alcoholism or starvation where carbohydrate stores are depleted, there is a high anion gap metabolic acidosis.[31]

With the upregulation of ketone production during prolonged fasting due to significant reduction in carbohydrate stores, most organs and tissues utilize ketone bodies as alternative source of energy during such period except the liver which lacks the enzyme beta ketoacyl-CoA transferase. Ketone bodies thus accumulate in plasma with an associated risk of ketoacidosis just as in patients with diabetes mellitus. Of the three predominate ketone bodies in humans, the beta-hydroxybutyrate is the most precise used to measure the severity of ketoacidosis in diabetic patients and the one measured and quantified by whole blood ketone test strips and serum laboratory tests since it can be confirmed in blood up to 24 hours prior to the appearance of acetone and acetoacetate in urine.[32]

For most, the normal range for ketones in serum is defined as below 0.5 mmol/L, ketonemia at a level of 0.6 mmol/L or higher, hyperketonemia above 1.0 mmol/L and ketoacidosis defined as levels 3.0 mmol/L or higher.[33]

In diabetic patients, blood ketone levels are used to predict the likelihood of a patient developing complications with levels 0.6mmol/L considered normal while those between 0.6-1.5 mmol/L, 1.6-3.0 mmol/L and above 3.0 mmol/L are considered low to moderate, high with risk of developing DKA, and likely DKA requiring immediate emergency management respectively.

2.1.4 The Role of Counter-regulatory Hormones on Glucose and Ketone Metabolism

In addition to insulin and glucagon actions on glucose and ketone metabolism during the fasting state, certain hormones and substances also play important roles. The counter-regulatory hormones actions are mainly in two folds; to increase glucose availability through increased glycogenolysis, lipolysis and gluconeogenesis and to inhibit the secretion and actions of insulin thereby reducing insulin-dependent glucose uptake in peripheral tissues. These actions ensure that glucose is readily available to the brain and other tissues dependent on glucose.

Cortisol, growth hormone, catecholamines and thyroid hormone are amongst the most important of these counter-regulatory hormones with their main purpose of ensuring a defense against hypoglycemia. As such, their actions are more pronounced during the fasted state when blood glucose level begins to fall.

Epinephrine is the most important catecholamine for glucose metabolism. Its release is stimulated and enhanced via the sympathetic nervous system changes with varying stimuli including hypoglycemia, anger, fear, tissue injury, excitement and surgical stress being responsible for such increased levels. Its actions are mostly sustained and mediated through beta-2 adrenergic receptors in various tissues and organs including the liver, kidneys, adipose tissues, and skeletal muscles. Its actions are most notable during acute recovery from hypoglycemia where in the liver it enhances glycogenolysis directly through cAMP mediated activation of phosphorylase and indirectly through increasing the availability of free fatty acids and other gluconeogenic substrates. Its action is more pronounced with stimulating renal gluconeogenesis than hepatic gluconeogenesis. In skeletal muscles, epinephrine along with glucagon increase glucose metabolism through increased lactate and pyruvate production and reduced glucose uptake by muscle cells. Lipolysis is increased through activation of hormone sensitive lipase with a resultant increase in free fatty acids and glycerol through the actions of epinephrine.[8,22]

Cortisol and growth hormone actions are seen in prolonged hypoglycemia stimulating the mobilization of sustained levels of amino acids and glycerol. Insulin secretion and insulin-dependent glucose uptake are also inhibited by cortisol and growth hormone. Growth hormone also stimulates the release of thyroxine which in turn increases glycogenolysis and glucose absorption from the intestines.[34]

2.2 Glycaemic Control in Pediatric Patients

The regulation of glucose metabolism is multifaceted to ensure plasma glucose levels are tightly controlled within a narrow range. This means the body homeostatic mechanisms quickly and effectively lower blood glucose levels during the fed state and up-regulate production during the fasted state through a balance of action between insulin as the main hormone for reducing blood glucose during the fed state and the counter-regulatory hormones glucagon, cortisol, growth hormone, thyroid hormone and catecholamine being the main glucose-raising ones. Glucose metabolism from stored sources usually depends on the amount of glycogen stored in the liver and muscles and the amount of gluconeogenic and ketogenic precursors from lipolysis, amino acids and other sources in the body. These stored precursors of glucose metabolism vary between adults and children and within individual age

groups. In a termed newborn with normal weight, there is a decline in plasma glucose from the maternal levels to about 2.8mmol/L within 2 hours after birth.

There is however a slow rise back to around 3.9mmol/L within days. Stored glycogen, gluconeogenesis and ketogenesis, through the actions of glucagon and catecholamines are the main sources that keep blood glucose in the newborn until the commencement of feeding. Growth hormone levels also increase leading to increased lipolysis and free fatty acid liberation. These actions in effect increase blood glucose production level far above those of adults with infusion studies in normal newborn suggesting basal glucose production rates at above 0.3-0.4mmol/kg/min.[35]

Anatomic and physiologic differences between the pediatric patients and adults still put them at risk despite the higher rate of glucose production. At birth the newborn brain is about 25 percent of that of the adult brain although newborns are mostly about 5 percent of adult weight. In addition to this proportionally large size of the brain, the cerebral metabolism of glucose also changes with advancing age where it begins as low as 60 percent of the rates in adults at birth but rapidly accelerates to above 200 percent of the adult values by age 5 years then tippers downward reaching adult values by adolescence.[36]

Compared with adults, infants and children also have a smaller amount of stored glycogen in liver and muscle cells which can be depleted within 12 hours in early infancy and 24 hours within late infancy and adulthood. Obligatory glucose requirements are higher in these children especially during early infancy due to the large proportion of the brain and the high growth rate of tissues and organs with an estimated rate of 0.5mmol/kg/min in infancy compared to adult rate of about 0.1-0.16mmol/kg/min.[8,29]

In smaller infants and children, the fasting state is also marked by slow response of glycogenolysis to glucagon, delayed maturation of gluconeogenic enzymes and impairment of ketogenesis from precursor free fatty acids. These factors predispose smaller infants to hypoglycemia and hyperketonemia than older children and adults.

2.2.1 Glycaemic State During Fasting

Hypoglycemia or hyperglycemia during the perioperative period following preoperative fasting is a serious concern for the pediatric patients. Hyperglycemia following pre-operative fasting is not as common as hypoglycaemic episodes in the pediatric patients. In fact, in normal healthy paediatric patients, hyperglycaemic episodes are rare. The study done by E. Mokaya however found 11.3% of her patients were hyperglycaemic at induction following preoperative fasting.[7]

Although there have been conflicting results from previous studies on the definition and incidence of hypoglycemia and hyperglycaemia in this population, the risk of serious complications remains. In fact, no universally agreed definition of either state currently exists especially in the non-diabetic population. WHO has defined hypoglycemia as a blood glucose level of less than 2.5 mmol/L while several other institutions use the cutoff blood glucose levels of 2.8 mmol/L to define hypoglycaemia.[37]

The American Diabetes Association (ADA) and the European Medicines Agency guidelines have used the threshold of 3.9 mmol/L as the cutoff blood glucose level to define hypoglycemia. The ADA has further classified hypoglycemia into three levels with blood glucose between 3.0 to 3.9 mmol/L being level one, less than 3.0 mmol/L being level two while level three is categorized as severe hypoglycemic events characterized by altered mental and or physical status requiring assistance for resolution.[38]

Even with these well-established guidelines, various institutions use different thresholds to define hypoglycemia. In settings where the definition is established, different thresholds are used based on the age of these patients as well as other factors including medical considerations surrounding each individual. Based on neurophysiologic and neurodevelopmental outcome studies, hypoglycemia was defined as a blood glucose level of less than 2.6mmol/L in neonates and less than 3.5mmol/L in childhood.[39,40]

This heterogeneity in the definition of hypoglycemia was also documented in the work done by Chakrapani et al in which they reviewed 109 RCTs to understand the severity and potential impact of heterogeneity in definitions of hypoglycemia used in diabetic research. In the same study, they found only 60 percent (66 studies) presented a defined cutoff of hypoglycemia with just 9 out of the 66 studies (14%) following the ADA/European Medicines Agency specified guidelines to define hypoglycemia at or below 3.9 mmol/L.[41]

The Ministry of Health of Kenya has recommended in the latest edition of the Basic Paediatric Protocols for up to five years old a threshold of less than 2.6 mmol/L for neonates and 3.0 mmol/L for older patients.[42]

Hyperglycaemia has been defined by WHO as fasting plasma glucose of 7.0 mmol/L or higher or whole blood glucose above 6.0 mmol/L.[43]

These definitions of hyperglycaemia were however done in diabetic patients as cutoffs in normal healthy individuals are yet to be agreed amongst internationally recognized bodies. Regardless of the heterogeneity in the definition and threshold for therapeutic interventions for hypoglycaemic and hyperglycaemic episodes in pediatrics, dysglycaemia has been shown to increase the risk of mortality and morbidity in pediatric patients with several studies

suggesting the neonates being at the highest risk of having severe effects from hypoglycemic episodes.[44]

Pre-term infants, those born small for gestational age, those with birth asphyxia, and those with hypothermia, sepsis or polycythemia are amongst such high-risk groups. These pediatric groups have been noted to have limited glycogen stores, immature gluconeogenic enzymes, impaired ability to mount a counter-regulation during fasting or starvation, inability to produce a ketogenic response, and a high energy demand.

Hypoglycemia is associated with increased risk of several adverse effects including cardiovascular events due to its proinflammatory and prothrombotic effects, severe neurological consequences including poor cognitive development, seizures and coma, poor or delayed emergence from anaesthesia, irritability and abnormal changes in vital signs during the perioperative period.[45,46,47,48]

In the RCT done by Sadhwani et al looking at the impact of tight glycaemic control and hypoglycaemia on the neurodevelopment of children following cardiac surgery found that moderate to severe hypoglycaemia was associated with worse neurodevelopmental outcomes.[49] Hyperglycaemia has also been noted to be associated with metabolic and acid-base disturbances, prolonged hospital stay, poor wound healing, renal and immune system adverse effects, higher infection rates, poor surgical outcomes and higher mortality rates. Patients with significantly higher intra-operative hyperglycaemic episodes have been found to have higher postoperative mortality and poor prognosis. A retrospective study done by O'Brien et al in 2009 found a statistically significant association between intra-operative hyperglycemia during cardiopulmonary bypass in paediatric patients undergoing cardiac procedures and postoperative bacteremia with 66.7% of the patients with postoperative infection being those with peak bypass glucose of at least 9.7mmol/L.[50]

Cochran et al also found higher mortality in pediatric patients with traumatic brain injury who had serum glucose of 14.8 or higher compared with those 7.5 mmol/L or lower with an admission serum glucose of 16.6 mmol/L or higher being uniformly associated with death.[51]

2.2.2 Ketone Levels in Pediatric Patient and the Perioperative Period

Although ketosis and ketoacidosis are a common finding in patients with diabetes having high blood glucose levels, non-diabetic ketosis and ketoacidosis can be found in pediatric patients with no history of diabetes presenting with normal or low blood glucose levels. Conditions of fasting, low carbohydrate states, high ketogenic diet with high fats contents and

low carbohydrates and extreme stress are amongst few of the precipitating environments that enhance high ketone metabolism as described in the physiology.

In normal paediatric patients, significant ketone metabolism serves as an alternative source of energy for vital organs including the brain. With lower stored glycogen and a higher metabolic rate then adults, paediatric patients are more prone to increasing ketone metabolism during the fasting hours and during severe stress including those of surgery and anaesthesia. It is said ketone levels can reach as high as 7.5 mmol/L during prolonged fasting in normal patients and up to above 25 mmol/L in those with diabetes.[52]

Although high blood ketone levels have been used in the management of refractory seizures due to their anti-oxidant effects, they can lead to metabolic acidosis with patients having a high risk of severe complications or even death. Klee et al found that ketosis on admission to PICU following cardiopulmonary bypass was an independent risk factor for an increased difference in arterial and venous oxygen saturation when they did a prospective observational study in children 6 months to 16 years undergoing cardiac procedures.[53]

In a retrospective case-series report done by Ke Bai et al between March 2009 and March 2015, they found 7 cases of non-diabetic ketoacidosis in children who all presented with severe dehydration, poor appetite and Kaussmaul breathing having blood ketones of over 3.1 mmol/L and a normal or low plasma glucose.[54]

A prospective study done by O'Donoghue et al at the Royal Hospital for Sick Children in the UK in 2006 using point of care testing (POCT) of blood ketones in 200 children under 13 years with various mixed medical issues found a strong correlation between blood ketone levels and admission. Of note, the study found that 48.9 percent of the children admitted after being seen in the emergency department and had a small but significantly higher median blood ketone level of 0.4 mmol/L (IQR 0.3-1.3 mmol/L) than the 54.3 percent discharged home with median ketone level of 0.2 mmol/L (IQR 0.1-0.7 mmol/L). Ketone levels also correlated well with decreased oral intake with a coefficient of determination of 0.25 and concluded that blood ketone levels can help predict admission to hospital in sick children.[55]

This also signifies the importance of rising blood ketone level in pediatric patients who have fasted or have poor oral intake due to their medical conditions and the risk of complications during the perioperative period. The metabolic acidosis resulting from these high blood ketone levels are usually treated with both insulin and glucose containing solutions instead of sodium bicarbonate with insulin known to inhibit lipolysis and reduce the production of ketone bodies while the glucose serves to improve blood glucose in these children who may have a normal or reduced plasma glucose levels.

2.2.3 Effect of Age/Weight on Glucose and Ketone Level during Fasting

The physiology of glucose metabolism showed younger children are more prone to developing hypoglycemia than older ones due to their high metabolic rate coupled with the lower stores of glycogen in the liver and their immature gluconeogenic enzymes. [1,2,4,7]

In the study done by van Veen Merel et al in 2011 to determine the reference values of metabolites involved in glucose homeostasis with retrospective analysis of 167 fasting tests performed on healthy children between 0-216 months old, they found a significant increase in plasma ketone body and significant decrease in plasma glucose level in all groups during the fasting period but noted a faster rise in ketone body levels and a faster decline in plasma glucose level in younger children 0-24 months than older children.[2]

The study done by Fatsani et al in 2020 in Malawi involving the cross-sectional review of feeding habits of 5131 children ages 0-17 years at the accident and emergency department reported that 2.1 percent of the children with blood glucose of less than 2.5 mmol/L and another 6.6 percent with values between 2.5 and 5 mmol/L. They found a statistically significant association between age of less than one month, age of less than five years and the presence of severe acute malnutrition and the occurrences of hypoglycemia in the review with severe acute malnutrition being the major factor for severe hypoglycemia.[56]

At KNH, E. Mokaya found the lowest blood glucose reading at induction in her study on intra-operative glycemic control in pediatric patients in 2017 to be amongst patients who were less than one year of age but found no significant difference in blood glucose reading at induction in relation to nutritional status between those with severely low birth weight and other categories of patients.[7]

Other studies however, have not found any statistically significant correlation between pre-operative fasting glucose levels and the age or weight of pediatric patients. The work done by Hajian et al on the impact of pre-operative fasting time on blood glucose and hemodynamics found no significant correlation between the blood glucose levels at the induction of anesthesia and weight of the patients based on age percentile and no significant difference in blood glucose level between children ages 3-7.5 years and those 7.6-12 years of age. The correlation between blood glucose at induction and body weight and age were not found to be statistically significant with Pearson correlation values at 0.016 and 0.098 respectively.[5]

It should however be noted that the patients studied were older children between the ages of three and twelve years which do not account for newborns and those below one year known to be at higher risk of hypoglycemia.

There are few research data available that associate the age and weight of pediatric patients with the level of blood ketone levels during fasting. One of such is the multi-center ramdomised controlled random order interventional crossover trail by Paul Wadwa et al in which children between 4-14 years with type 1 diabetes mellitus were placed in two age groups, 4-9 year and 10-14 years. Elevated morning blood ketone level, defined as 0.6 mmol/L or higher was found during control nights in 10 percent of the patients 4-9 years of age compared to 2 percent the older ones 10-14 years while a higher frequency of 13 percent versus 2 percent was found during the intervention nights in the younger age group when compared to the older children following the use or suspension of an automated nocturnal predictive low glucose suspend (PLGS) system. They also observed longer durations of pump suspension resulted in higher percentages of elevated morning ketones in the younger age group but not the older age group.[57] These findings show a varying degree to which the weight and age of these pediatric patients may have on glucose and ketone levels during the fasting period.

2.3 The Fasting Guidelines in Children

Pre-operative fasting has existed as far back as the nineteenth century when it was suggested as a means of reducing the unpleasant feeling of anesthesia associated vomiting. This practice has been modified several times as existing evidence continues to discourage prolonged hours of fasting as it has been shown to have deleterious effects. Following several reports of aspiration during general anaesthesia, including the 66 cases reported by Mendelson in obstetric patients, the nil per os (NPO) from midnight recommendation was enforced throughout major institutions during the 1970s.[58]

Subsequent modifications in preoperative fasting with guidelines from the American Society of Anesthesiologists (ASA) in 1998 and 2011, the European Society of Anaesthesiology (ESA) in 2011 and the Scandinavian Society of Anaesthesiology and Intensive Care (SSAI) in 2003 have seen widespread adaptation of recommendations to avoid solid food for 6 hours, breast milk for 4 hours and clear fluids for 2 hours prior to the induction of anaesthesia.[59,60,61] Although these guidelines have been adopted to prevent or reduce the risks of pulmonary aspiration of gastric contents, more recent evidence has however not shown the need for more prolonged fasting time. A prospective multicenter study done in the UK where the 6-4-2 guideline is widely used found a very low incidence of pulmonary aspiration in paediatric patients at 2.0 and 2.2 per 10,000 cases for elective and emergency respectively.[62]

The Anaesthesia Practice in Children Observational Trail (APRICOT) study, another multicenter prospective study of severe critical events in paediatric anaesthesia, noted that despite aspiration of gastric contents, there was not a single case of ICU admission and no long term morbidity or mortality was associated with aspiration.[63]

Another multicenter trial done by Beach et al found similar incidence of aspiration between fasted and none-fasted paediatric patients with more than 139,000 anaesthetics and procedural sedations.[64]

In addition to the low risk of pulmonary aspiration, multiple studies on the physiology of gastric emptying in paediatric patients have provided additional information leading to more modifications in the fasting guidelines. Gastric emptying of solid foods is described as a zero-elimination kinetics; thus, solids pass from the stomach to the duodenum at a constant rate while gastric emptying of clear fluids follows first-order kinetics with elimination done exponentially. These observations have shown that even a 200 ml drink of clear fluid can be reduced to 25 ml within 30 minutes to an hour based on the elimination half-life of 10 or 15 minutes.[61]

Schmitz et al cross over study using magnetic resonance imaging (MRI) of gastric content volume following the ingestion of clear sugared fluid in paediatric patients also showed gastric contents were similar to baseline volumes of overnight fasting one hour after ingestion of a 3ml/kg volume.[65]

Multiple studies have also shown lowered gastric emptying time for breast milk and formula milk with only marginally longer transit time for infant formula compared to breast milk.[66,67]

Even with the widespread use of the ASA, ESA, ESAIC 6-4-2 recommendations for fasting in many centers including KNH, pediatric patients continue to be starved for longer periods than needed thus predisposing them to increased risks of hypoglycaemia, metabolic acidosis, irritability, dehydration, cardiovascular instability, hunger, thirst, and general discomfort.[68,69]

Between 2017 and 2022, many of the major anaesthesia societies updated their guidelines to reflect research findings on prolonged fasting especially in the pediatric age groups. In most of these revised guidelines, fasting times for clear fluid and breast milk were modified and reduced to 1 hour and 3 hours respectively to reflect findings from the physiology of gastric emptying and the risks of pulmonary aspiration of these gastric contents.[70,71,72]

In fact, there was no extra risk of pulmonary aspiration amongst patients taking clear fluids one hour before anaesthesia and those following longer fasting durations, there were less nausea and vomiting, less thirst, less hunger and anxiety, more compliance and better physiologic and metabolic effects found in the 6-3-1 and 6-4-1 fasting groups than those

fasting for longer durations.[69] A summary of current guidelines and recommendations from major anaesthesia societies are attached in appendix IV

2.3.1 The Average Pre-Operative Fasting Time

Regardless of the fasting guidelines and institutional policies on pre-operative fasting, there seems to be a pattern of prolonged fasting time across many institutions. In the cross-sectional study conducted by Hussein et al in 2021 at the Tikur Anbessa Specialized Hospital in Ethiopia found the mean duration of fasting in hours for solid food, breast milk and clear fluids were 13.25, 7.75 and 12.31 respectively with all 258 pediatric patients undergoing elective surgical procedures in the study fasting for more than 4 hours for clear fluids. [3]

In another cross sectional survey conducted in several selected public hospitals in 2020 by Yimer et al looking at the adherence to pre-operative fasting guidelines in pediatric patients less than 17 years old going for elective surgical procedures also reported prolonged fasting times with the mean fasting time for clear liquids, breast milk and solids being 10 +/- 4.03 hours, 7.18+/- 2.26 and 13.5+/- 2.76 with only 10 percent of the 279 patients in the study adhering to the fasting guidelines of all three categories of meal types.[73]

Similar findings have been seen across many other institutions regardless of which ever tools or guidelines are being used. Between 2008 and 2013, Gregor et al conducted eleven prospective clinical audits at the University of Malawi to monitor the preoperative fasting situation of pediatrics patients undergoing surgical procedures at the teaching hospital. Regardless of training conducted during those audits for nurses and caregivers on fasting guidelines, the mean fasting time across all audits was 8.48 hours with range of 13.48 in 2008 to 6.52 hours in 2013.[74]

Another prospective observational study done by Dennhardt et al in Germany in 2015 amongst pediatric patients between zero to thirty-six months on the impact of pre-operative fasting time on blood glucose concentration, ketone bodies and acid-base balance found a mean fasting time of 7.8+/- 4.5 hours with a range of between 3.5 to 20 hours with deviation from the fasting guidelines of between 2 to 14 hours.[75]

Prolonged fasting times beyond established guidelines have been reported even at the Kenyatta National Hospital with Mokaya showing in her research on intra-operative glycaemic control in pediatric patients undergoing surgical procedures a mean duration of fasting of 9.97 +/-3.7 hours with significant increases in fasting duration across the age groups, 6.25 in infants, 9.8 hours in children one to four years and 13.7 hours in older children.[6]

The most recent findings from KNH came from the study done by B. Hangalla in 2022 on the comprehension and compliance to pre-operative fasting instructions by primary caregivers of pediatric surgical patients that showed median fasting times for clear fluids, breast milk, infant formula and solids at 9 hours, 7 hours, 7 hours and 12.5 hours respectively. There were even longer ranges of fasting times for emergencies versus elective procedures for clear fluids, breast milk, infant formula and solids at 4-13 hours vs 6-14 hours, 4-13 hours vs 6-14 hours, 6-7 hours vs 7-9 hours and 6-17 hours vs 8-16 hours respectively. [76]

In the United Kingdom, El-Sharkawy et al conducted a prospective audit of pre-operative fasting time at five National Health Service (NHS) Trust with the review of 343 surgical patients over a two month period where they found the overall median fasting times of 16.1 hours for foods and 5.8 hours for clear fluids with about 73 percent and 21 percent of participants fasting more than 12 hours for foods and clear fluids respectively while those fasting for emergency procedures fasted longer for clear fluids and food than those going for elective procedures with median times for clear fluids at 13.0 vs 4.9 hours and for foods at 22.0 vs 15.6 hours respectively.[77]

Another prospective cross-sectional study done in 2016 by Nouman I. Alvi at the Aga Khan University Hospital in Pakistan involving 102 pediatric patients up to age 16 years undergoing planned surgical procedures found 96 percent did not follow the pre-operative fasting guidelines with the median fasting time for solid at 12.0 hours with range between 6 to 48 hours while that of clear fluids was 9 hours with range of 1 to 48 hours.[78]

Across regions and institutions, adherence to fasting guidelines seems almost impossible especially in centers with large patient flow or fewer theatre spaces. In fact, factors including inadequate or improper pre-operative fasting instructions from healthcare providers, change in theatre list sequences, delays in surgical procedures and lack of proper training on recent updates amongst healthcare providers are some of the reasons of such prolonged fasting times. This was shown in an audit done by B.G. Arun and Grace Korula in 2013 in a tertiary care hospital where 50 children under 15 years for elective surgeries were reviewed in a cross-sectional study and found prolonged pre-operative mean fasting [times] for solids and water at 11.25 hours and 9.25 hours respectively with 74 percent of the prolonged fasting being attributed to incorrect nurses' instructions on the wards and 32 percent due to change in surgical schedule.[79]

In another prospective observational study conducted at the Red Cross War Memorial Children's Hospital in Cape Town in 2020 by A. J. Kouvarellis et al also found the mean fasting durations for clear liquids, breast milk, formula milk and solid food to be 8.0, 7.1, 8.8

and 13.9 hours respectively with factors such as inadequate fasting instructions, poor adherence to fasting orders, delays in procedures and prolonged fasting to promote flexibility in theatre time being amongst the most common reasons.[80]

2.3.2 The Impact of Pre-operative Fasting Time on Glucose and Ketone Levels:

Most of the literature has pointed to pre-operative fasting times far beyond what have been recommended for clear fluids, milk and solid foods across several hospitals around the world. Despite these prolonged fasting times, the actual impact on blood glucose levels and ketone bodies varied across studies. In the study done by E. Mokaya in 2017 at KNH, she found hypoglycemic incidence of 15.2 percent at induction among the 145 pediatric patients with significant correlation between the duration of fasting and induction blood glucose (correlation coefficient of 0.26) with a reduction of 0.08mmol/L for each additional hour of fasting.[6]

In the study conducted by Hussein et al involving a cross-sectional review of 258 pediatric patients undergoing elective surgical procedures who had fasted more than the required fasting duration, 26.2 percent were found to be hypoglycemic with blood glucose level less than 3.0 mmol/L and patients who fasted more than 8 hours being 2.3 times more likely of being hypoglycemic than those fasted less than 6 hours. When compared to those who fasted before midnight, pediatric patients who fasted after morning were 95 percent less likely to be hypoglycemic during anesthesia.[3]

Although the correlation between fasting time and blood glucose was not significant (correlation coefficient, r =0.19) in the study by Dennhardt et al, it however showed a statistically significant correlation between fasting time and blood ketone levels (r = 0.58) with two of the three children who developed hypoglycemia having blood glucose level below 2.8mmol/L also with mean deviation from the guidelines for more than two hours.[55]

The correlation between prolonged fasting time and the development of significant blood ketone level was also established in the study done by Dennhardt et al when they found that 23 out of the 100 pediatric patients reviewed had ketone levels between 0.6-1.5mmol/L while 7 had results above 1.5mmol/L. Notably, 27 out of the 30 patients with these blood ketone levels had mean deviation from the fasting guidelines by more than 2 hours.[55]

Similar results were reported by N. Maekawa et al in 1993 when 105 pediatric patients were given apple juice and randomly selected to fast at intervals of 2-, 4-, and 12-hour periods with a significant rise in total ketone bodies for both the 4- and 12-hour fasting groups.[81]

Although there were no significant differences between the three groups at induction in relation to glucose concentration, gastric pH or volume, plasma cortisol and triglyceride levels following administration of apple juice prior to fasting, however, the author found a significant higher concentration of total body ketones and non-esterified fatty acid in the 4-

and 12-hour fasting groups than the 2-hour fasting group. Hajian et al found no significant correlation between the duration of pre-operative fasting and blood glucose level in the cross-sectional study of 50 pediatrics patients done in Iran (Pearson correlation for solids and liquid at -0.101 and 0.001 respectively).[5]

Although many of the above studies have shown variable links between hypoglycemia and prolonged fasting, it is believed that glucose concentration was kept within normal or near normal in many of the patients due to the compensatory mechanisms of glucose metabolism during fasting. Ketones on the other hand, have been significantly increased with correlation to prolonged fasting equally demonstrated in the study above, thus begging the question of ketones being a much better show of prolonged fasting than glucose concentration in the pediatric age patients. In fact, in many of the studies above, the incidence of hypoglycemia was significantly lower than those of ketonemia or ketoacidosis with patients presenting with near normal glucose concentration also having significant increases in their blood ketone levels.

2.4 Measurement of Glucose and Ketone

Although the gold standard of ketone measurement is mass spectrometry, the method seems very expensive and usually inaccessible for routine clinical practice. Point of care (POC) measurement of blood glucose and ketone bodies are now widely being used in clinical settings especially in emergency and primary care facilities with diabetic patients being the main subjects. The routine use of POC glucose measurement is more common than that of blood ketone level in most clinical care areas. The three main ketone bodies resulting from fatty acid metabolism include acetoacetate, beta-hydroxybutyrate and acetone. Unlike urine ketone measurement which uses nitroprusside reaction to give a semi-quantitative measure of acetoacetate in urine, the POC ketone meter uses whole venous, arterial or capillary blood to measure 3-beta-hydroxybutyrate level.[82]

When compared to urine ketone measurement, POC ketone measurement has been shown to be more effective and accurate in the diagnosis and monitoring of ketone level in patients with ketonemia to a considerable extent. In a systematic review done by Klocker et al in 2013 comparing the effectiveness of serum or capillary beta-hydroxybutyrate with urine acetoacetate in the prevention and management of patients with type 1 diabetes found testing for beta-hydroxybutyrate being more effective than urine testing for acetoacetate in the reduction of emergency department visits, hospitalization and time to recovery for patients with DKA.[83] Another randomized clinical trial conducted by Laffel et al in 2006 involving 123 patients with type1 diabetes between ages 3-22 years assessing the effectiveness of managing the sick days of the participants using POC blood 3-beta-hydroxybutyrate

measurement compared to urine ketone found a significantly lower incidence of emergency assessment/hospitalization in those measuring blood ketone than the urine ketone group (38/100 patient-years vs 75/100 patient-years) with blood ketone group having a significantly higher frequency of measuring during the sick days than those in the urine ketone group (276 of 304 episodes or 90.8% vs 168 of 274 or 61.3%). [84]

A one-year retrospective study conducted in 2004 by Pierre et al comparing the sensitivity, specificity and predictive value of ketonuria and ketonemia in the diagnosis of ketoacidosis involving 355 hyperglycemic patients also found the two tests to have 100% sensitivity at two-cross cut off for ketonuria and 3.0 mmol/L for ketonemia but lower specificity for ketonuria at 77% than ketonemia at 94%.[85]

The study also found both measurements had similar negative predictive value of 100% when excluding ketoacidosis at ketonuria of one-cross or ketonemia of lower than 3.0 mmol/L while the best positive predictive value for ketonuria was at the tree-cross cutoff (26%) and that for ketonemia at 5 mmol/L cut off (100%). The findings from these studies correlate well with the review done by Ketan Dhatariya in 2016 with comparison of two measurement modalities where he noted the urine measurement was cheaper, did not require special training to perform the test, painless to perform but had a lower specificity and sensitivity than the blood ketone measurement as well as delays in dehydrated patients who may not produce urine with urine ketone level mostly being an average of bladder content over time and not an actual reflection of blood ketone level.[86]

Although the blood ketone measurement showed a better prospect in the diagnosis and management of diabetic patients, he noted the POC ketone measurement was more expensive than the urine strips, needed special training for those using it, had a wide coefficient variation at higher blood ketone readings of more than 3.0 mmol/L and 5.0 mmol/L based on the machine being used.

Compared with the standard laboratory measurement of blood ketones which uses spectrophotometric method of measurement, the POC ketone measurement of beta-hydroxybutyrate using beta-hydroxybutyrate dehydrogenase coupled with electro-chemical detection has proven to have good correlation up to a certain limit. In a study done by Voulgari et al in 2010 where they compared the performance of the capillary blood glucose-ketone POC meter using the Precision-Xtra device (Abbot Laboratories, Abingdon, UK), to measured serum glucose and biochemical parameters using an automatic analyzer employing the enzymatic end-point spectrophotometric method and urine ketones using the semi-quantitative assay in the diagnosis of DKA in patients with type 2 diabetes, they found serum

and capillary beta-hydroxybutyrate results highly correlated (r = 0.99) and serum and capillary glucose significantly correlated (r = 0.86) in the 450 patients seen in the emergency room.[87]

The study also found the capillary ketonemia had the highest performance for the diagnosis of DKA with sensitivity, specificity and positive predictive value of 99.87 %, 92.89% and 92.89% respectively compared to serum ketonemia (specificity 90.45%, sensitivity 88.65%, positive predictive value 87.76%) and ketonuria with sensitivity of 89.89%, specificity of 52.73% and positive predictive value of 41.47%. Rewers et al also found a good agreement between bed-side venous beta-hydroxybutyrate measurement using the Precision-Xtra (Abbott Diabetes Care, Abbott Park, IL) and the serum measurement using a reference laboratory method (Cobas Mira Plus; Roche Diagnostics, Indianapolis, IN) in 68 children in DKA with Pearson's correlation of 0.92 which was confirmed using the Bland-Altman plot analysis.[88]

A prospective comparative study done in South Africa by Coetzee et al in 2015 with 61 consecutive samples from suspected patients with DKA also evaluated and compared capillary ketone via POC hand-held ketone meter with a gold-standard manual enzymatic method using plasma ketones and found the two methods had good correlation (r = 0.95) with POC method having sensitivity and specificity of 100% and 89% for DKA (β-OHB>3 mmol/L), while at levels<1 mmol/L sensitivity was 100% and specificity 87.5%.[89]

These correlations were also demonstrated by Raweewan et al in 2014 comparing the efficacy of capillary beta-hydroxybutyrate measurement using the Abbott OpiumXceed compared to standard laboratory serum biochemistry using the nitroprusside reaction to distinguish DKA from non-DKA patients with correlation between capillary and serum ketone being statistically significant (r= 0.72).[90]

The diagnostic accuracy of POC ketone measurement is affected by several factors including hematocrit levels, vitamin C and ketone levels above 6.0 mmol/L.[91]

Currently no internationally recognized reference method of blood glucose exists but the Center for Disease Control and Prevention (CDC) has recommended glucose measurement method based on isotope dilution gas chromatography-mass spectrometry (IDGC-MS).[92]

Samples for glucose measurement usually include whole blood (capillary, venous or arterial) and plasma with majority detecting glucose levels based on enzymatic reactions involving either glucose oxidase, hexokinase or glucose dehydrogenase.[93]

Due to the physiological difference between glucose measurement in whole blood and in plasma, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) has recommended all glucose measurement devices to report results in plasma values with whole blood value being multiplied by a factor of 1.11 to obtain such plasma value.[94,95]

Point of care glucose measurement devices use whole blood and have been clinically validated by several studies and have been in clinical use for several decades.[96] In addition to the differences in the diagnostic accuracies between various devices based on the matrix and method used for measurement, patient factors such as hematocrit, pH, hydration and fasting status, blood oxygen, site of sample collection and maltose level also have varying effects, with devices said to be most inaccurate at the extremes of blood glucose in the body.[97,98]

The IFCC, the American Diabetes Association (ADA) and the International Organization for Standardization (ISO) 15197 have all recommended various margins of errors and deviations from standard reference measurements ranging from 5% to 20% of reference values to ensure various devices are within acceptable accuracies to actual blood glucose measurements.[99,100,101]

2.5 Study Justification

Anesthesia Societies and organizations around the world continue to provide guidance through guidelines, recommendations and updates for clinical practice to ensure the safety of patients during the perioperative period and beyond. Specific categories of patients including those of the pediatric age are at particular risks hence the need to continuously modify existing practices based on research evidence. Many centers have created, adopted, modified and adjusted one or more of these guidelines to fit their local and or regional realities. The complexities surrounding theatre allocations, adjustments in the order of theatre listing either due to intra-operative complications or equipment and supply issues, poor or improper preoperative instructions and understanding between anesthesia providers, nurses and patient caregivers, inadequate staffing and resources in high volume centers, are just a few of the challenges that result into inefficiencies in the implementation of fasting guidelines and recommendations around the world.

For most patients, circulating blood glucose from their last meals, stored glycogen and more importantly, the body's ability to use alternative energy source, provide the physiologic stability during this period. With limited glycogen stores and high body metabolic rates, many of the pediatric patients rely on alternative sources of energy including fatty acid metabolism and the use of ketones for physiologic functions perioperatively.

Due to the physiological differences in glucose metabolism between the pediatric and adult age groups, pediatric patients remain at high risk of complications of poor glycemic control with hyperglycemic or hypoglycemic episodes, high ketone levels, dehydration, thirst, hypotension, intra-operative instability and poor emergence during reversal of anesthesia as well as prolonged hospital stay.

Anaesthesia providers at the KNH continue to use fasting guidelines from the American Society of Anaesthesiologists with modifications from other leading world anesthesia societies based on individual cases to guide the safety of patients during the perioperative period. Like many other resource limited, high volume surgical centers around the world, KNH still faces many of the challenges above. To reduce and minimize the perioperative risk to patients, point of care RBS testing in addition to clinical assessment, remains the main tool available for rapid decision making. Even for patients with normal or near normal RBS, the risk of having abnormally high ketones and clinically significant acidosis still remains due to the homeostatic mechanisms that kick in during the fasting period.

As such, the routine use of additional assessment modality and tool such as POC blood ketone testing during the perioperative period, aimed at enhancing the ability of anesthesia and other healthcare providers to have additional rapid, safe and cost-effective means of assessment of at-risk patients is an important reason for this research. Data from this research has the potential of enhancing care for the pediatric patients in other acute care settings including the emergency/casualty area and intensive care units at KNH.

In addition, there is still a paucity of data that provides a clear understanding of the association between preoperative fasting time, blood glucose and ketone levels in the pediatric patient group. This study intends to provide data which will not only enhance the current clinical practice and assessment of at-risk patients during the perioperative period but also provide a baseline for future research on the association between glucose and ketones in specific subgroups.

2.6 Research Question

Is there any association between pre-operative fasting times, blood glucose concentration and ketone levels in pediatric patients presenting for surgeries at the Kenyatta National Hospital?

2.7 Study Objectives

2.7.1 Broad Objectives

To determine the association between pre-operative fasting time and the level of blood glucose and ketones in pediatric patients ages 0-13 years undergoing surgical procedures at the Kenyatta National Hospital (KNH) main and satellite theatres.

2.7.2 Specific Objectives:

a. To determine the association between pre-operative fasting time and glucose concentration in paediatric patients undergoing surgical procedures at KNH

b. To identify the association between pre-operative fasting time and blood ketone levels in children undergoing surgical procedures at KNH
c. To determine the duration of pre-operative fasting in pediatric patients undergoing surgical procedures at the Kenyatta National Hospital
d. To associate demographic variables (age, weight, gender) and type of meal with the level of glucose and ketone in the fasted pediatric patients undergoing surgical procedures at the Kenyatta National Hospital.

3.0 CHAPTER THREE: STUDY METHODS

3.1 Study Design

This study was an analytical cross-sectional study of a convenient sampling of pediatric patients 0-13 years presenting for both elective and emergency surgical procedures at the Kenyatta National Hospital with pre-operative fasting of any duration. The study was undertaken between March and April 2023.

3.2 Study Setting

The Kenyatta National Hospital is the largest and main national referral hospital in Kenya located in Nairobi, with 2000 bed capacity, over 6000 staff members, 50 wards and 22 out-patient clinics. There are 24 theatres including 12 main theatre suites with the remaining being specialized satellite theatres. Pediatric patients are admitted through the accident and emergency department, the various specialized outpatient clinics or as referrals from other centers directly to the various wards or directly to the surgical theatre based on the nature of the intended surgery.

Between January and June 2022, a total of 1400 pediatric surgical cases were performed with an average of about 234 cases per month. These cases came from various subspecialties including ophthalmology, Ear-Nose-Throat (ENT), general pediatric surgery, pediatric urology, cardiothoracic and vascular surgery, neurosurgery, and orthopedic surgery. About 65% of these surgeries were elective procedures while 35 percent were done on an emergency basis with the main theatres undertaking 71% of the total number of cases. The remaining 29% were carried out within the satellite theatres.

Anesthesia providers reviewed these patients prior to the scheduled day of surgery for elective cases or on the same day for emergency procedures on their admitted wards or at the theatre receiving areas respectively. The current research was conducted at all the main theatres and the ENT and ophthalmology satellite theatre areas providing emergency and elective surgical care to pediatric patients at the Kenyatta National Hospital.

3.3 Study Population

All pediatric patients undergoing elective and urgent surgical procedures at Kenyatta National Hospital who met the inclusion criteria made up the study group. They ranged in age from 0 to 13 years. Patients are admitted to the pediatric wards at KNH if they are under the age of 13 and to the adult wards if they are over the age of 14, respectively.

3.3.1 Inclusion Criteria:

All pediatric patients admitted at the Kenyatta National Hospital who met the below inclusion criteria were included in the study:

a) Pediatric patients classified as I and II as per the ASA guideline as attached in appendix VII

3.3.2 Exclusion Criteria

These included:

a) Patients on ketogenic diet for weight modification
b) Patients on vitamin C supplementation prior to surgery
c) Patients with endocrine disorders such as diabetes mellitus
d) Patients with traumatic brain injuries
e) Patients on intravenous fluids administration during the preoperative fasting period
f) Patients without signed consent from parents/next of kin

3.4 Sample Size Determination

Sample size calculation was done with the use of the formula for correlation analysis[102]

$$n=\left(\frac{Z_{\propto}+Z_{\beta}}{C(r)}\right)^2+3$$

Where, $C(r)=\frac{1}{2}\ln\ln\left(\frac{1+r}{1-r}\right)$

n = desired sample size

r = correlation coefficient from a previous study done by Dennhardt et al[57] for fasting time and blood glucose was, r=0.19

$Z_{\propto}$ = value from standard normal distribution corresponding to desired confidence level - two tail (Z=1.96 for 95% CI)

Z_{β} = value from standard normal distribution corresponding to 80% power (0.842)

Substituting the values; $C(r)=\frac{1}{2}\ln\ln\left(\frac{1+0.19}{1-0.19}\right)=0.19$

$$n=\left(\frac{1.96+0.842}{0.19}\right)^2+3=220$$

The sample size required was 220 paediatric patients but 222 patients were included in the study. The patients were sampled from the main theatres, ENT and ophthalmology satellite theatres.

3.5 Recruitment and Consenting Procedures

On the day or night before surgery, paediatric patients scheduled for surgery were identified using the theatre list. The paediatric patients were approached through their next of kin/parents by the principal investigator and the research assistant either in the wards (elective patients) or the theatre receiving areas (emergency patients). The research was explained and a request for participation made which was then followed by explanation of a detailed consent/assent in both English and Swahili to ensure full understanding by the caregiver and the patient. Once the consent for participation had been signed, the principal investigator and the research assistant then assessed each patient to ensure they met the inclusion criteria prior to the administration of the research questionnaire on the day of surgery. There were 225 patients recruited and 222 analyzed after meeting the inclusion criteria.

3.6 Variables

The demographic data included the age, gender and weight of the participants while clinical data included the diagnosis, type of surgical procedure, the urgency of the procedure (elective/emergency), the fasting time (time from last oral intake to time of sample collection at induction of anaesthesia in hours and minutes), type of last meal (clear fluids, breast milk, other milk or solid food), blood glucose level in millimoles per litre and blood ketone level in millimoles per litre. Baseline vital signs including blood pressure, heart rate, respiratory rate and skin temperature were also included.

3.7 Data Collection Procedure

The data were collected using a questionnaire by the principal investigator and the research assistant. The demographic data and part of the clinical history were collected and filled at the receiving area from the parent or next of kin and the patient file. The participants were then taken to the operating theatre with all required pre-anesthesia checks completed. Once on the operating table, basic monitoring including SpO2, ECG, skin temperature probe, and blood pressure cuff were connected and initiated using clinically validated patient monitors.

As gas induction with sevoflurane/halothane or intravenous induction with propofol began, blood sample collection was performed. The patient's heel or fingertip was cleaned using alcohol swabs twice to ensure aseptic collection of blood samples. The alcohol was allowed to air dry for up to 30 seconds prior to pricking. A single-use disposable lancet needle was used for pricking the patient.

The initial drop of blood was cleaned off and the heel/fingertip squeezed to get the needed sample of 0.5 microlitre of blood for each of the two samples per patient. Using corresponding strips for POC blood glucose and blood ketone measurement, the first blood sample taken was tested for ketone assessment while the second was used for blood glucose assessment to ensure consistency. The results were displayed on the portable handheld blood glucose and ketone measurement device within 5-10 seconds of sampling. Using a clean dry cotton swap, the site of sample collection was gently compressed to allow hemostasis and a strapping applied over it to ensure no inadvertent bleeding.

The results were then recorded on the data sheet as indicated for each participant. As per the ADA and the European Medicines Agency guidelines, hypoglycemia was defined as a blood glucose reading of less than 4.0 mmol/L while hyperglycemia was defined as blood glucose of 7.0 mmol/L or higher.[38,41.43] A blood ketone reading of 0.6 mmol/L or higher was considered significant ketonemia, while hyperketonemia was defined as result of 1.0 to 2.99 mmol/L and result of 3.0 mmol/L and above was defined as ketoacidosis. These definitions were based on multiple studies in paediatric diabetic patients.[32,33]

3.8 Blood Glucose and Ketone Measurement Tool

The current study used the Freestyle Optium Neo Blood Glucose and Ketone Monitoring System by Abbott Diabetes Care Inc./Abbott Laboratories Limited. This is a handheld glucose and ketone measurement device which was clinically validated and approved by both the Food and Drug Administration (FDA) and the European Union (EU) and meets the ISO 15197:2013 compliance with proven superior accuracy when compared with other POC measurement devices.[103,104,105]

The device uses about 0.5-1 microlitre of whole blood from capillary, venous and arterial origin through an electrochemical biosensor to display results on an LCD screen within 5-10 seconds in a range from 0.1-9 mmol/L for blood ketones and the range of 1.1-17.8 mmol/L for blood glucose reading.[89, 106,107]

Results outside these limits read as “LO” or “HI” to denote low or high respectively. There was no coding required and quality control testing was done every 7 days at the KNH central biochemistry laboratory by a trained laboratory personnel with calibration done at the opening of each batch of test trips as per the user manual.

3.9 Ethical Considerations:

a) Approval from the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee was gotten prior to commencement of the study.
b) Enrolment and participation in this study was voluntary with option to leave at any time during the research.
c) Written informed consent/assent in English and Swahili was obtained from the parents/next of kin and study participant.
d) All abnormal findings including hypoglycemia, hyperglycemia and or clinically abnormal blood ketone levels, were reported to the primary doctor/anaesthetic team immediately with appropriate interventions initiated as per protocol.
e) There was no incident during the study requiring documentation and reporting to KNH-UoN ERC and KNH.
f) No financial cost was incurred by the participants for any investigations required for the study.
g) There was no monetary benefit for participants, their parents or next of kin for being a part of this research. Benefits of adequate health education on fasting, blood glucose and ketone levels was made available to the participants.
h) To ensure confidentiality and security of patient information, serial coding was used on questionnaires with stored data only accessible to the research team.

3.10 Data Management

All data from the questionnaires were carefully inspected for completeness by the principal investigator. Thereafter, the data were cleaned and entered into a data base using password secured google excel spreadsheet and then transferred to SPSS version 26 for statistical analysis with the help of a qualified statistician.

The Shapiro-Wilk test was used to test for normality. Description of the study population was done through summary of the social, demographic, and clinical characteristics which were presented as frequencies and percentages for categorical variables, while for continuous variables, mean with standard deviation was used for normal distribution and median with interquartile ranges for non-normal distribution. Associations between preoperative fasting time and blood glucose concentration, preoperative fasting time and blood ketone levels and the relationship between blood glucose and ketone were analyzed with the use of Pearson correlation to determine the strength and direction of the associations. The results were presented using scatter plots. These associations were also presented as equations with the

use of linear regression. The duration of pre-operative fasting was analyzed and presented as mean with standard deviation and as median with inter quartile range. Association between demographic characteristics with glucose and ketone levels were done with the use of Pearson correlation for continuous variables and independent t-test or ANOVA for categorical variables. Statistical significance was then tested at 5% (p-value ≤ 0.05). Findings were presented using graphs and tables.

3.11 Dissemination of Results

The findings from this research are being made available and accessible to the below listed:

a) The Department of Anaesthesia, UON
b) The Faculty of Medicine, College of Health Sciences, UON
c) The Graduate School, UON
d) The Kenyatta National Hospital
e) UON Library
f) Peer Review Scientific Journals for publication.

4.0 CHAPTER FOUR: RESULTS

Table 1:Characteristics of paediatric patients undergoing surgical procedures at the Kenyatta National Hospital (n=222)

	Frequency (percentage)
Age	
0.0 – 4.0 weeks	13 (5.9)
1.1 – 11.9 months	39 (17.6)
1.0 – 5.0 years	122 (55.0)
5.1 – 10.0 years	35 (15.8)
>10 years	13 (5.9)
Sex	
Male	125 (56.3)
Female	97 (43.7)
Weight (kg)	
<3.0	6 (2.7)
3.0 – 5.0	22 (9.9)
5.1 – 10.0	49 (22.1)
10.1 – 20.0	103 (46.4)
20.1 – 30.0	32 (14.4)
>30.0	10 (4.5)

The lowest age was 1 day and the highest was 13.0 years. A Shapiro-Wilk test indicated ages and weights were not normally distributed ($p<0.001$). The median age was 3.0 (IQR 1.2 – 5.0) years. Majority of the patients were male (56.3%). The minimum weight was 2.3kg and the maximum was 65.0kg. The median weight was 13.0 (IQR 9.0 – 18.0) kg.

Table 2:Areas of Surgical Subspecialties of Paediatric Patients Undergoing Surgical Procedures at the Kenyatta National Hospital

Surgical subspecialties	**Frequency (percentage)**
General Paediatric Surgery*	56 (25.2)
Ophthalmology	52 (23.4)
ENT	51 (23.0)

Plastics	23 (10.4)
Neurosurgery	16 (7.2)
Orthopaedics	13 (5.9)
Maxillo Facial	8 (3.6)
Cardiothoracic	3 (1.4)

***General paediatric surgery includes paediatric urology & gastro-intestinal surgical procedures**

Table 3:Type of Last Meal Taken by Paediatric Patients Undergoing Surgical Procedures Before Commencement of Preoperative Fasting at the Kenyatta National Hospital

Type of last meal	Frequency (percentage)
Solids	103 (46.4)
Breast milk	56 (25.2)
Other milk*	49 (22.1)
Clear fluids	14 (6.3)

***Other milk includes non-human milk, yogurt, tea (containing milk products)**

Table 4:Systolic Blood Pressure at Induction of Anaesthesia of Paediatric Patients Undergoing Surgical Procedures at the Kenyatta National Hospital

Systolic BP**	Frequency (percentage)
Normal	206 (92.8)
Low	9 (4.1)
High	7 (3.2)

****systolic blood pressure measurement in mmHg with cut-offs as defined per age group according to the American Heart Association's definition of hypotension.**

Table 5:Glycaemic Status at Induction of Anaesthesia of paediatric Patients Undergoing Surgical Procedures at the Kenyatta National Hospital

Glycaemic Status (mmol/L)	Frequency (percentage)
Euglycaemia (4.0 – 7.0)	155 (69.8)
Hypoglycaemia (2.5 – 3.9)	52 (23.4)
Severe Hypoglycaemia (<2.5)	13 (5.9)
Hyperglycaemia (>7.0)	2 (0.9)

Table 6:Blood Ketone Status at Induction of Anaesthesia of Paediatric Patients Undergoing Surgical Procedures at the Kenyatta National Hospital

Blood ketone status (mmol/L)	Frequency (Percentage)
Normal <0.6	130 (58.6)

*Ketonemia (0.6 – 0.9)	38 (17.1)
Hyper Ketonemia (1.0 – 2.99)	38 (17.1)
Ketoacidosis (≥3.0)	16 (7.2)

***Significant ketonemia**

4.1 Objectives

4.1.1 Objective One

To determine the association between pre-operative fasting time and blood glucose levels of paediatric patients undergoing surgical procedures at the Kenyatta National Hospital.

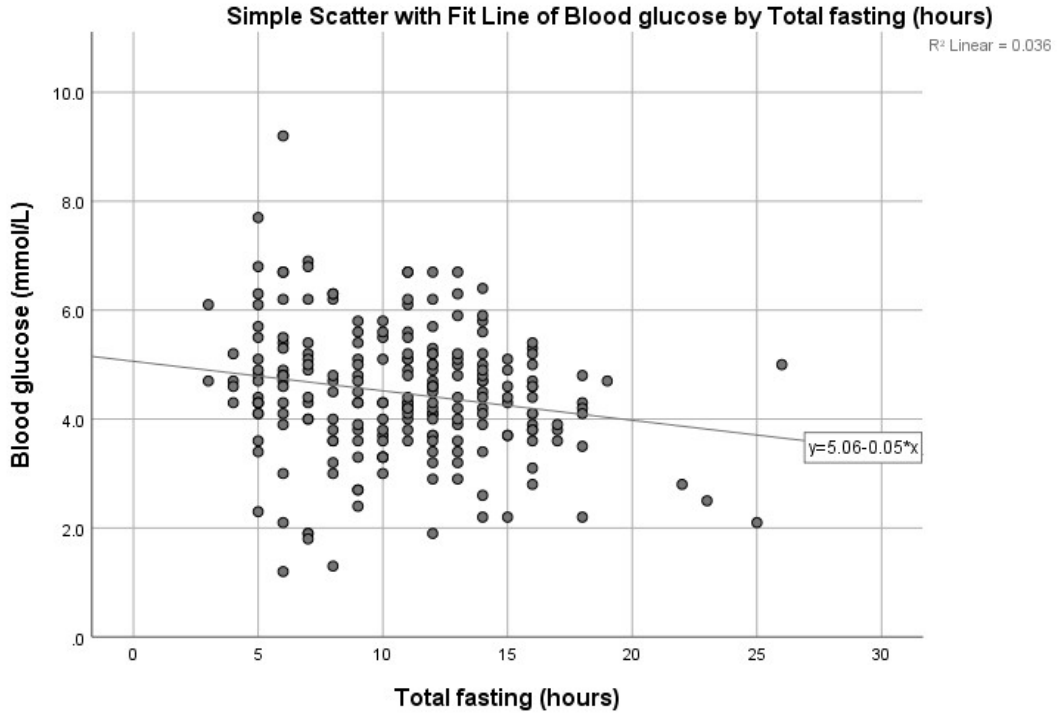

Figure 1:The Association between Preoperative fasting time and blood glucose levels at induction of anaesthesia in pediatric patients undergoing surgical procedures at the Kenyatta National Hospital

Figure 1 shows that as total fasting time increases the level of blood glucose decreases, and a Pearson correlation analysis indicates there was poor correlation which was statistically significant. (r = -0.190, p=0.04). A simple linear regression where y is the dependent variable (blood glucose) and x is the independent variable (fasting time in hours) shows that for every 1 unit increase of time (i.e. hour), the blood sugar drops by 0.05 mmol/L.

4.1.2 Objective Two

To determine the association between pre-operative fasting time and blood ketone levels in paediatric patients undergoing surgical procedures at the Kenyatta National Hospital.

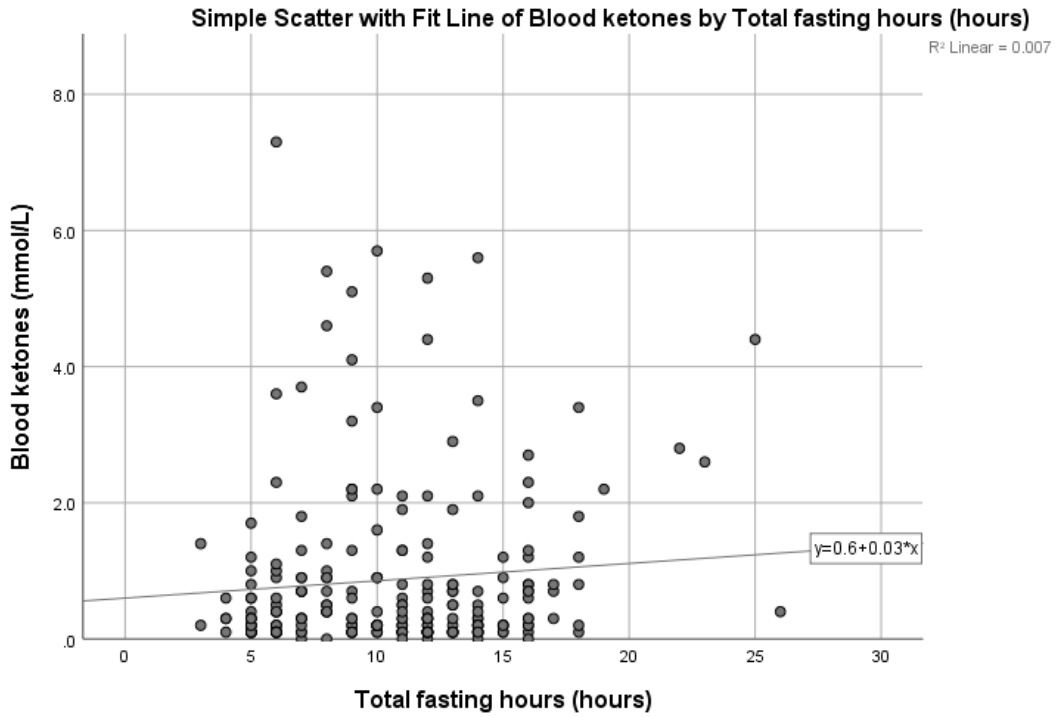

Figure 2:The association between preoperative fasting time and blood ketone levels at induction of anaesthesia in paediatric patients undergoing surgical procedures at the Kenyatta National Hospital

Figure 2 shows that as the total fasting time increases the level of blood ketones increases, and a Pearson correlation analysis indicates there was poor correlation which was not statistically significant. (r = -0.086, p=0.202). A simple linear regression where y is the dependent variable (blood ketones) and x is the independent variable (fasting time in hours) shows that for every 1 unit increase of time (i.e. hour), the blood ketones increase by 0.03 mmol/L.

4.1.3 Objective Three

To associate demographic variables (age, weight, gender) and type of meal with the level of blood glucose and blood ketone in the fasted paediatric patients undergoing surgical procedures at the Kenyatta National Hospital.

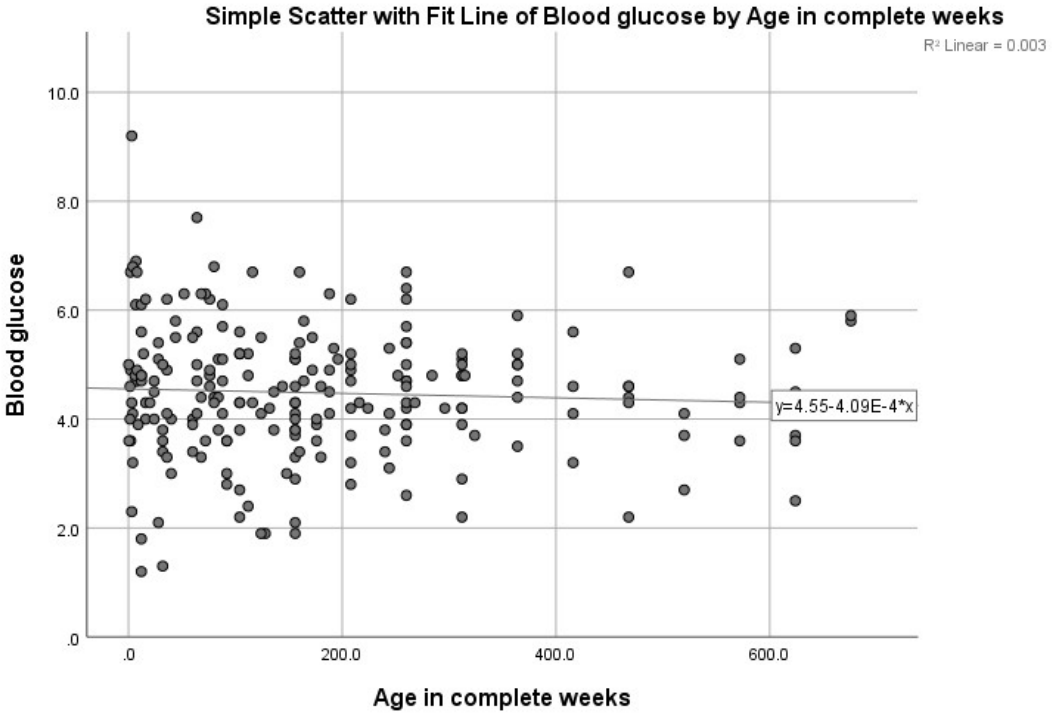

Figure 3:The association between age and blood glucose level at induction of anaesthesia in fasted paediatric patients undergoing surgical procedures at the Kenyatta National Hospital

Figure 3 shows that as the age increases the level of blood glucose decreases, and a Pearson correlation analysis indicates there was poor correlation which was not statistically significant. (r = -0.057, p=0.396). A simple linear regression analysis, where y is the dependent variable (blood glucose) and x is the independent variable (age in complete weeks), shows that for every 1-unit increase age (i.e., 1 week), the blood glucose decreases by 0.000409 mmol/L.

Figure 4:The association between weight and blood glucose level at induction of anaesthesia in fasted paediatric patients undergoing surgical procedures at the Kenyatta National Hospital

Figure 4 shows that as the weight increases the level of blood glucose decreases, and a Pearson correlation analysis indicates there was poor correlation which was not statistically significant. (r = -0.041, p=0.542). A simple linear regression analysis, where y is the dependent variable (blood glucose) and x is the independent variable (weight in kg), shows that for every 1-unit increase weight (i.e., 1 kg), the blood glucose decreases by 0.00539 mmol/L.

Table 7:The association between gender and blood glucose levels at induction of anaesthesia of fasted paediatric patients undergoing surgical procedures at the Kenyatta National Hospital

	Mean ± SD	p-value
Male	4.5 ± 1.2	0.407
Female	4.4 ± 1.1	

An independent sample t-test showed no statistical difference in the blood glucose level between the gender (p=0.407).

Table 8:The association between type of last meal and blood glucose level at induction of anaesthesia in fasted paediatric patients undergoing surgical procedures at the Kenyatta National Hospital

	Mean ± SD	p-value
Clear fluids	4.6 ± 1.2	0.710
Breast milk	4.6 ± 1.4	
Other milk	4.5 ± 1.3	
Solids	4.4 ± 1.0	

An Analysis of Variance (ANOVA) shows no statistical difference in the blood sugar levels between the meals (*p=0.710*).

Figure 5:The association between age and blood ketone level at induction of anaesthesia in fasted paediatric patients undergoing surgical procedures at the Kenyatta National Hospital.

Figure 5 shows that as the age increases the level of blood ketones decreases, and a Pearson correlation analysis indicates there was poor correlation which was statistically significant. (r = -0.158, p=0.019). A simple linear regression, where y is the dependent variable (blood

ketones) and x is the independent variable (age in weeks), shows that for every 1 unit increase of age (i.e. 1 week), the blood ketones decreases by 0.00117 mmol/L.

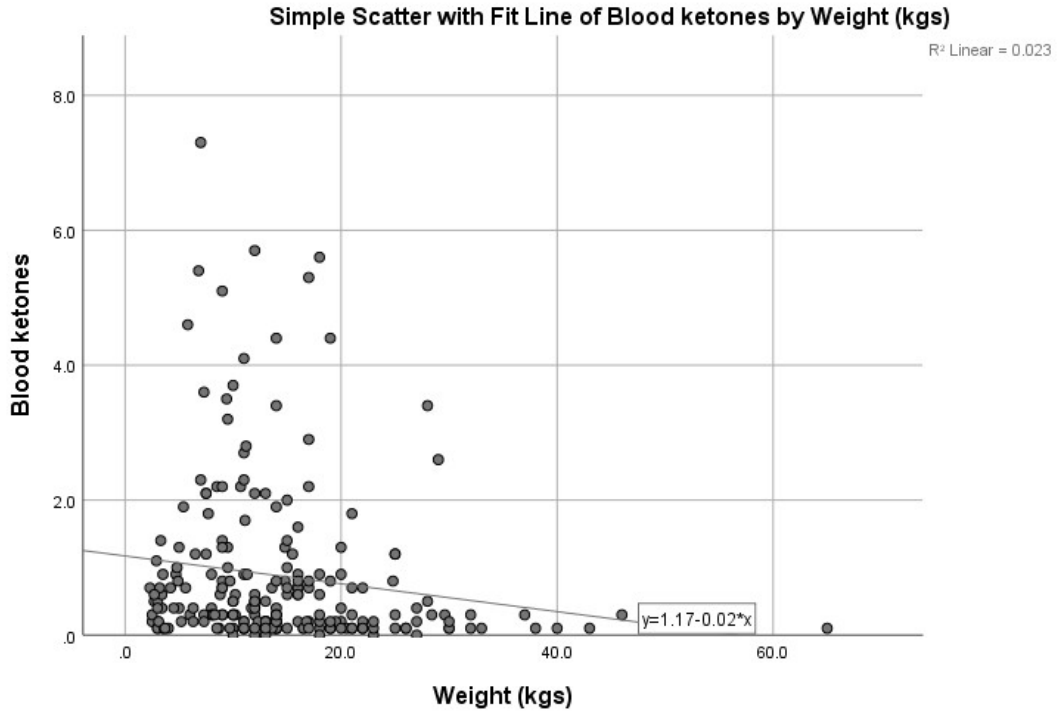

Figure 6:The association between weight and blood ketone level at induction of anaesthesia in fasted paediatric patients undergoing surgical procedures at the Kenyatta National Hospital

Figure 6 shows that as the weight increases the level of blood ketones decreases, and a Pearson correlation analysis indicates there was poor correlation which was statistically significant. (r = -0.151, p=0.024). A simple linear regression analysis, where y is the dependent variable (blood ketones) and x is the independent variable (weight in kg), shows that for every 1 unit increase of weight (i.e., 1 kg), the blood ketones decrease by 0.02 mmol/L.

Table 9:The association between gender and blood ketone level at induction of anaesthesia in fasted paediatric patients undergoing surgical procedures at the Kenyatta National Hospital

	Mean ± SD	p-value
Male	0.85 ± 1.2	0.732
Female	0.91 ± 1.3	

An independent sample t-test to determine if there were difference in the mean blood ketone levels between the genders shows no statistical difference in the blood ketone levels between the gender (*p=0.732*)

Table 10:The Association between the type of last meal and blood ketones level at induction of anaesthesia in fasted paediatric patients undergoing surgical procedures at the Kenyatta National Hospital

	Mean ± SD	p-value
Clear fluids	0.7 ± 0.7	0.525
Breast milk	1.1 ± 1.5	
Other milk	0.9 ± 1.2	
Solids	0.8 ± 1.1	

An Analysis of Variance (ANOVA) run to determine differences in the mean blood ketone levels between the type of meals found no statistical difference in the blood ketone levels between the meals (*p=0.525*).

4.1.4 Objective Four

To determine the duration of preoperative fasting in paediatric patients undergoing surgical procedures at the Kenyatta National Hospital.

Table 11:The preoperative fasting duration at induction of anaesthesia in paediatric patients undergoing surgical procedures at the Kenyatta National Hospital

	Median (IQR)	Min	Max
Fasting time (hours)	11.0 (7.0 – 14.0)	3.0	26.0

A Shapiro-Wilk test indicated that the fasting times were not normally distributed ($p<0.001$).

Table 12:The preoperative fasting duration for the type of last meal at induction of anaesthesia in paediatric patients undergoing surgical procedures at the Kenyatta National Hospital

Type of last meal	n	Mean fasting in hours, (Mean ± SD)
Clear fluids	14	9.1 ± 5.6
Breast milk	53	7.4 ± 3.2

Other milk	49	9.3 ± 2.5
Solids	102	13.7 ± 2.8

Table 13:Frequency and Percentage of Deviation from the preoperative fasting guidelines in Paediatric Patients Undergoing Surgical Procedures at the Kenyatta National Hospital

Meal types	Number of children on meal type	Number deviating from guidelines	Percentage deviating
Clear fluids	14	14	100.0%
Breast milk	56	53	94.6%
Other milk	49	49	100.0
Solids	103	102	99.0%

Table 14:Mean deviation of the preoperative fasting duration from the fasting guidelines for each type of last meal taken in paediatric patients undergoing surgical procedures at the Kenyatta National Hospital

Type of last meal	n	Mean fasting in hours, (Mean ± SD)	Mean deviation, (Mean ± SD)
Clear fluids	14	9.1 ± 5.6	7.1 ± 5.6
Breast milk	53	7.4 ± 3.2	3.4 ± 3.2
Other milk	49	9.3 ± 2.5	5.3 ± 2.5
Solids	102	13.7 ± 2.8	7.7 ± 2.8

4.2 Secondary Findings

Table 15:Characteristics of fasted paediatric patients undergoing surgical procedures at the Kenyatta National Hospital found to have hypoglycemia at induction of anaesthesia

	Frequency (%), *(n=65)*
Age	
0.0 – 4.0 weeks	4 (6.2)
1.1 – 11.9 months	10 (15.4)
1.0 – 5.0 years	38 (58.5)
5.1 – 10.0 years	9 (13.8)
>10 years	4 (6.2)
Sex	
Male	31 (47.7)
Female	34 (52.3)

Weight (kg)	
<3.0	2 (3.1)
3.0 – 5.0	4 (6.2)
5.1 – 10.0	16 (24.6)
10.1 – 20.0	29 (44.6)
20.1 – 30.0	11 (16.9)
>30.0	3 (4.6)

The secondary findings looked at the characteristics of hypoglycaemic patients. The lowest age was 3 days and the highest was 12.0 years. A Shapiro-Wilk test indicated that the ages and weights were not normally distributed ($p<0.001$). The median age was 3.0 (IQR 1.3 – 5.0) years. The minimum weight was 2.7kg, and the maximum was 46.0kg while the median weight was 13.0 (IQR 9.0 – 19.0) kg.

Table 16:The urgency of surgical procedures among fasted paediatric patients who had hypoglycaemia at induction of anaestheisa

Urgency	Frequency (%), *(n=65)*
Elective	57 (87.7)
Emergency	8 (12.3)

Table 17:pre-operative fasting duration of paediatric patients undergoing surgical procedures at the Kenyatta National Hospital who had hypoglycaemia at induction of anaesthesia

	Median (IQR)	Min	Max
Fasting time (hours)	12.0 (9.0 – 15.0)	5.0	25.0

Table 18:Mean fasting duration and mean deviation from the fasting guidelines per each type of last meal in fasted paediatric patients undergoing surgical procedures at the Kenyatta National hospital who had hypoglycaemia at induction of anaesthesia (n=65)

	n	Mean fasting in hours, (Mean ± SD)	Mean deviation, (Mean ± SD)
Clear fluids	4	13.0 ± 6.7	11.0 ± 6.7
Breast milk	12	6.9 ± 1.4	2.9 ± 1.4
Other milk	17	9.4 ± 2.4	5.4 ± 2.4

Solids	32	14.7 ± 3.2	8.7 ± 3.2

Figure 7:Association between Blood ketones and blood glucose levels among fasted paediatric patients undergoing surgical procedures at the Kenyatta National Hospital who had hypoglycaemia at induction of anaesthesia.

Figure 7 shows that as the blood glucose increases the level of blood ketones decreases, and a Pearson correlation analysis indicates there was moderate correlation which was statistically significant. (r = -0.425, p<0.001). A simple linear regression analysis, where y is the dependent variable (blood ketones) and x is the independent variable (blood glucose), shows that for every 1 unit increase of blood glucose, the blood ketones decrease by 1.02 mmol/L.

5.0 CHAPTER FIVE: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1 Discussion

The study aimed to demonstrate the association between preoperative fasting time, blood glucose concentration and blood ketone levels in paediatric patients undergoing surgical procedures at the Kenyatta National Hospital. The total number of participants were 222 patients, and the study was conducted from March to April 2023.

The study found a male predominance of 125 (56.3%) compared to 97 females (43.7%). These patients were spread across several surgical specialties with general paediatric surgery (56), ophthalmology (52), and ENT surgery (51) making up 71.6 percent (159) of the cases while cardiothoracic surgery had the least number of patients at 1.4 percent (3).

The link between preoperative fasting time, blood glucose and blood ketone levels has been noted to be variable. While many studies have shown poor association between preoperative fasting hours and blood glucose concentration, some have found significant hypoglycaemia and hyperketonemia in fasted paediatric patients. There was a significant amount of the patients in this study who were hypoglycaemic at induction of anaesthesia with a prevalence of 29.3 percent (65 patients), with 5.9 percent being severely hypoglycaemic, having blood glucose levels below 2.5 mmol/L at induction of anaesthesia.

In Ethiopia, Hussien et al also found 26.3 percent of the paediatric patients to be hypoglycaemic when they did a cross-sectional study on preoperative fasting time and its association with hypoglycaemia during anaesthesia in paediatric patients undergoing elective procedures.[3] There was a lower prevalence of hypoglycaemia (15.2 percent) found in the study by E. Mokaya in 2017 at KNH.[7]

The different prevalence of hypoglycaemia in these studies clearly shows the variable link between preoperative fasting time and blood glucose levels in the paediatric population but could also be due to the heterogeneity in the sample sizes, preoperative fasting times and demographics of the study subjects. Moreover, the lack of consensus on the cut-offs of blood glucose levels to define hypoglycaemia and hyperglycaemia could also explain these differences. The current study used a cut-off of 3.99 mmol/L or lower to define hypoglycaemia as per the guidelines from the American Diabetes Society and the European Medicines Agency while other studies have used WHO or local guidelines with much lower cut-offs, hence the lower prevalence seen compared to this study.[37, 38, 42]

For the 65 patients who were observed to be hypoglycaemic, the median fasting duration was 12.0 (IQR: 9.0-15.0) hours with deviation observed for each type of last meal. Notably in this group of hypoglycaemic paediatric patients, the mean fasting time and deviation from the fasting guidelines in those who took clear fluids as a last meal were 13.0 +/-6.7 hours and 11.0 +/-6.7 hours respectively. Although the expectations and requirements for patients who take clear fluid dictate the lowest preoperative fasting duration, prolonged fasting time for clear fluids have been observed in multiple studies including the study at KNH in 2022 by B. Hangalla where the median fasting time for clear fluid was 9.0 (IQR 7.75-11.25) hours.[76]

Although the study found blood ketone increased by 0.03 mmol/L for each hour of fasting, there was however a poor correlation between preoperative fasting time and blood ketone level which was not statistically significant ($r = -0.086$, $p=0.202$). This differs from the findings by Dennhardt et al study in which there was good correlation between preoperative fasting time and blood ketone levels at induction of anaesthesia ($r = 0.58$, $p< 0.001$).[75]

These differences could also be explained by the heterogeneity in the sample size, demographics, and range of preoperative fasting time. For example, this study covered patients from zero to 13 years comprising both elective and emergency surgical procedures while the one by Dennhardt et al involved children 3 years or younger and only elective cases. Although there are limited studies on preoperative fasting and blood ketone levels in non-diabetic paediatric patients, higher blood ketones have been noted in younger diabetic children than older ones following periods of overnight fasting as noted in the multi-center ramdomised controlled random order interventional crossover trial by P. Wadwa et al where Ketone production in children 4-14 years with type 1 diabetes were studied.[57]

The study found younger children 4-9 years had higher ketone levels than the older ones, a result which could explain the good correlation between fasting time and ketone levels as seen in the study by Dennhardt et al which covered mostly younger children 3 years and younger when compared to the current study with children up to 13 years. Regardless of the poor correlation in this study, it was demonstrated clearly that the level of blood ketone increased with increasing fasting time as seen in other studies by Maekawa et al and Dennhardt et al.[75, 81] In addition, high ketone level was found in 41.4 percent (92) of the patients with 16 of them (7.2%) having ketoacidosis. This is clinically significant since the management of non-diabetic ketoacidosis in children slightly differs from those of DKA where both insulin and glucose are recommended to treat the former.

The preoperative fasting time was prolonged, both the overall median fasting hours and those for individual types of last meal taken by the patients. The overall median fasting time was 11.0 (IQR 7.0-14.0) hours. Similar findings of prolonged preoperative fasting durations were found in multiple studies including the ones done by E. Mokaya on the Intra-operative Glycaemic Dynamics in Paediatric Patients at KNH with mean fasting duration of 9.97 (+/- 3.7) hours and Dennhardt et al in Germany on the impact of preoperative fasting times on blood glucose concentration, ketone bodies and acid-base balance with mean fasting duration of 7.8 +/-4.5 hours and a range of 3.5 to 20 hours.[7,75]

In the prospective audits done by Gregor et al in Malawi between 2008 and 2013 on excessive fasting time: still an under-addressed challenge for paediatrics and anaesthesia, the mean fasting time was found to be 8.48 hours.[74] Prolonged preoperative fasting for individual types of meal was also seen in the cross-sectional study done on the adherence to preoperative fasting guidelines and associated factors among paediatric surgical patients in Ethiopia by Yimer et al where the mean fasting times were 10 +/- 4.03 hours, 7.18 +/- 2.26 hours and 13.5 +/- 2.76 hours for clear fluids, breast milk and solid foods respectively.[73] These findings compared similarly with this research which found fasting times for clear fluids, breast milk, other milk and solids where 9.1 (+/- 5.6) hours, 7.4 (+/- 3.2) hours, 9.3 (+/- 2.5) hours and 13.7 (+/- 2.8) hours respectively.

In addition, A.J. Kouvarellis et al in South Africa, Dennhardt et al in Germany and Hussien et al in Ethiopia also found similar results in their studies denoting prolonged mean fasting times for each category of food during preoperative fasting.[3, 75, 80] At KNH, B. Hangalla found the median fasting durations of 9.0 hours for clear fluids, 7.0 hours for breast milk, 7.0 hours for infant formula, and 12.5 hours for solid food in 2022 when she studied the comprehension and compliance to preoperative fasting instructions by primary caregivers of paediatric patients.[76] These prolonged fasting times also show persistent deviation from current recommendations on paediatric fasting prior to surgical procedures. The current research found that 98.2 percent (218 patients) deviated from the fasting guidelines with only 1.8 percent (4 patients) noted to have fasted accordingly. Nouman et al did a prospective, cross-sectional survey of preoperative fasting of paediatric surgical patients in Pakistan and found 96 percent of the 102 patients deviated from the fasting guidelines.[78]

These results were comparable to the study done by Yimer et al which found only 10 percent of 279 (90 percent deviation) participants adhered to the fasting guidelines for all categories of meal types and the one done by Hussien et al where the found 100 percent deviation of more than 4 hours for clear fluids in all 258 patients paediatric patients going for elective surgical procedures.[3, 73,

The prolonged preoperative fasting time and deviation from established fasting guidelines in this study could be explained by the challenges faced at the Kenyatta National Hospital. The number of limited theatre allocations due to inadequate theatre spaces usually means emergencies and some elective procedures compete for the available theatres resulting to prolonged waiting periods. The lack of an officially documented fasting policy means anaesthesia providers, nursing staff and surgeons are likely to give different fasting instructions based on the guidelines they may be more familiar with.

Individualized preoperative fasting instructions to reflect the actual surgical time seems almost impossible because of the unpredictable nature in the order of theatre listings hence a generic fasting instruction for all to ensure patients are not cancelled or postponed. This may reflect either limited knowledge on updated guidelines among doctors and nursing staff, inadequate staffing to appropriately supervise preoperative fasting patients, poor communication between the anaesthetists, surgeons, and nursing staff when adjustments to the theatre listing are made, or a general fear of their patient being cancelled from the theatre list due to food intake.

Even in events of recognized prolonged fasting by nursing and anaesthesia providers, access to commercially prepared/prepackaged glucose-containing clear fluids for children is another challenge at the Kenyatta National Hospital. Late commencement of cases in theatre along with prolonged turnaround time either from complications intraoperatively, inadequate logistics for timely patient transport from the wards to theatre or from the table to the recovery areas could mean patients who are lower down the theatre listings may run the risk of fasting for longer periods than those at the top. Lastly, early feeding on the eve of surgery with many of the children last intake prior to bedtime and an entire night of fasting before surgery may also explain the prolong preoperative fasting periods in this study.

Modifications of preoperative fasting guidelines have been done in recent years by recognized anaesthesia societies around the world after results from multiple studies showed the detrimental effects of prolonged preoperative fasting in children during the perioperative period. However, prolonged preoperative fasting times continue to exist in multiple centers. The current guidelines have lowered preoperative fasting time considerably and encouraged oral clear fluid intake up to 1-2 hours before surgery, breast milk between 3-4 hours, nonhuman milk fasting for 4 hours while solid food is recommended for 6 hours.[66, 67, 68, 69] Despite these modifications, prolonged preoperative fasting periods have been observed across many facilities, both resource limited and resource abundant settings.[3, 6, 73, 74, 75, 76]

The study also shows that for every one-hour increase in preoperative fasting time, the blood glucose dropped by 0.05 mmol/L. However, analysis shows there is poor correlation between preoperative fasting time and blood glucose level which was statistically significant (r = -

0.190, p =0.04). This result can also be seen in the study by E. Mokaya with a poor correlation (r = 0.26) between the duration of fasting and blood glucose at induction and those found by Dennhardt et al (r =0.19, p>0.05) and Hajian et al where there was also a poor correlation between duration of fasting and blood glucose at induction of anaesthesia (r = -0.101, p= 0.487).[5, 6, 75]

Although this study clearly demonstrated a significant drop in blood glucose level with each additional fasting hours, the poor correlation could be explained by the fact that compensatory glucose metabolism can be influenced by several factors including age, weight, glycogen store, level of activities during the fasting period and the level of stress response in each individual patient. As such, prolonged preoperative fasting may have varying effects ranging from euglycaemia to severe hypoglycaemia or hyperglycaemia.

High ketone level was found in 41.4 percent (92) of the patients with 16 of them (7.2%) having ketoacidosis. Although the study showed blood ketone increased with increasing fasting time and for each hour of fasting, the blood ketone increased by 0.03 mmol/L, there was however a poor correlation between preoperative fasting time and blood ketone level which was not statistically significant (r = -0.086, p=0.202).

This differs from the findings by Dennhardt et al in which there was good correlation between preoperative fasting and blood ketone levels at induction of anaesthesia (r = 0.58, p< 0.001).[55] These differences could also be explained by the heterogeneity in the sample size, demographics, and range of preoperative fasting time. For example, this study covered patients from zero to 13 years comprising both elective and emergency surgical procedures while the one by Dennhardt et al involved children below 3 years and only elective cases. Regardless of the poor correlation in this study, it was demonstrated clearly that the level of blood ketone increased with increasing fasting time as seen in other studies by Maekawa et al and Dennhardt et al.[55, 81]

There was poor association between the blood glucose levels and the weight and age of the patients and no statistical difference in the glucose levels between genders and the types of last meal in this current study. These findings are similar to the findings from the work done at KNH by E. Mokaya and the one by Hajian et al.[5, 6]

These findings also speak to the varying nature of the body's response to fasting and glycaemic regulations in various age groups and the complexities of each group is affected regardless of physiologic reserves. Fatsani et al however found lowered glucose levels in smaller children with a significant correlation between lower age and the development of hypoglycaemia.[56]

Although this was also a cross-sectional study, the setting was the accident and emergency area with severe acute malnutrition being the major determining factor for hypoglycaemia unlike the current study involving ASA I and II patients with none associated with the diagnosis of malnutrition. The correlation between blood ketone levels, age, weight and gender was also found to be poor in this study, a result similar to other studies although higher blood ketone levels were found in younger children by Wadwa et al.[57]

Although this study found poor correlation between preoperative fasting time, blood glucose and blood ketone levels following statistical analysis, a further looked at the data showed a clear inverse relationship between hypoglycaemia and high blood ketone levels in the paediatric population which may be of clinical significance. For every 1 mmol/L increase in blood glucose level, the blood ketone dropped by 1.02 mmol/L. This study found a correlation between hypoglycaemia and ketone level which was statistically significant ($r = -0.425$, $p<0.001$).

In patients with hypoglycaemia, significant deviation from the preoperative fasting time was observed with mean deviation for breast milk being the lowest at 2.9 +/- 1.4 hours while the mean for clear fluids was the longest at 11.0 +/- 6.7. Most of the hypoglycaemic patients were those who took solids (32/65 or 49.2%), a result also reflected in the age group between 1-5 years who made up 58.5% of the hypoglycaemic patients. These results are clinically similar to findings from Hussein et al where paediatric patients who fasted more than 8 hours were 2.3 times more likely to develop hypoglycaemia than those who fasted for less than 6 hours.[3] Regardless of the patient age, weight or gender and the complexities involved in glucose metabolism, preoperative fasting time seems to be the most significant determinant of clinically concerning ketonemia and hypoglycaemia throughout multiple studies.[3, 5, 6, 55, 56, 81]

5.2 Conclusion

The median fasting time among paediatric patients undergoing surgical procedures at the Kenyatta national hospital was 11.0 (IQR 7-14) hours with 98.2% of the participants deviating significantly from the current fasting recommendations. This is not in keeping with the international documented guidelines of preoperative fasting. The correlation between preoperative fasting time and blood glucose concentration and blood ketone levels was not strong. Notwithstanding this, hypoglycaemia and ketoacidosis may occur in these patients when subjected to prolonged fasting time. This is clinically significant as it may complicate the perioperative care and recovery of paediatric patients if not recognized and managed appropriately.

5.3 Recommendations

To ensure a reduction in preoperative fasting time, clear policy on preoperative fasting, which includes an updated guideline, should be developed by the Kenyatta National Hospital. Emphasis should be placed on individualized preoperative fasting instructions and management including making glucose-containing clear fluids readily available. These policies should be disseminated to all stakeholders involved with paediatric preoperative fasting. Additional trainings, through continuous medical education (CMEs), for all healthcare providers involved in the perioperative management of surgical patients at the Kenyatta National Hospital should be done with emphasis on individualized preoperative fasting. Preoperative blood glucose and blood ketone testing should be routine for all elective and emergency paediatric surgical patients.

5.4 Limitation of The Study

The information regarding the preoperative fasting events was from the parents/guardians or next of kin as is the practice in the Kenyatta National Hospital.

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APPENDICES

Appendix I: Parental Consent and Study Explanation (English version)

STUDY TITLE: The Association between Preoperative Fasting, Blood Glucose Concentration and Blood Ketone Level in Paediatric Patients Undergoing Surgical Procedures at the Kenyatta National Hospital

Study Site

The Kenyatta National Hospital Main and Satellite Theatres

Principal Investigator/Institutional Affiliation: Dr. Gonkarnue Nuan Department of Anaesthesia, University of Nairobi

Introduction

I am conducting research on children going for surgical procedures at the Kenyatta National Hospital on the association between preoperative fasting time, blood glucose concentration and blood ketone levels in children. We have developed this consent form to help us explain the entire research process to you as the parent/guardian and the child including potential risks, harm, discomfort, or benefits the research shall have. You can ask us questions before deciding to give or not to give consent for your child to be a part of the study which will include a total of 220 children between 0-13 years of age.

Purpose Of the Study

The research will find out whether preoperative fasting time will cause any change in the blood glucose concentration and blood ketone levels in children. To do this, I shall take information including the weight, gender, age, surgical diagnosis, underlying disease condition, time of last meal and type of last food eaten. In addition, the blood pressure, pulse rate, oxygen saturation, temperature and respiratory rate will be measured before your child is put to sleep inside the operating theatre. Once he/she is asleep, a very small amount of blood will be taken from the fingertip or toe of your child using a tiny disposable needle in a very careful manner to measure the blood sugar and blood ketone level. All information collected will be copied on a special form for each child taking part in the study which shall be analyzed by me and my team.

Participation

If you do agree for your child to be a part of this research, it will be purely voluntary and you can withdraw at any point. You will not incur any additional cost due to this study other than the one related to the cost of care at the Kenyatta National Hospital. The study will not

interfere, affect or delay the management of your child and there will be no financial benefit to your child for participating.

Risk of Participation

There are very minimum risks associated with participation in this study and none shall change or alter the planned management of your child.

Confidentiality

All the information collected about your child will be strictly confidential and only accessible to me and the research team and will be protected at all times.

Research Result & Dissemination:

The findings from the study will be shared with the University of Nairobi, the Kenyatta National Hospital and other experts through appropriate formal platforms.

Consent:

I, _____ parent/guardian/next of kin of _____, resident of _____ hereby give a written consent for my child to voluntarily participate in the study "the association between preoperative fasting time, blood glucose concentration and blood ketone level in paediatric patients undergoing surgical procedures at the Kenyatta National Hospital".

I have been fully informed and understood the research processes and all of my questions and concerns have been addressed. I also understand that I have the right to withdraw from the research at any given point.

Signed:_____ Date:_____

Investigator's Declaration:

I have fully explained to the parent/guardian or next of kin about the study and have addressed all questions and concerns raised.

Signed:_____

Date:_____

If you have questions or need more information about this study, you can contact the following

Principal Investigator:

Dr. Gonkarnue Nuahn
Registrar, Department of Anaesthesia
University of Nairobi, Nairobi, Kenya
Email: g.nuahn@students.uonbi.ac.ke
Mobile: 0757161011

Supervisors Contacts:

Dr. Nancy N. Okonu
Paediatric Anaesthetist, Consultant Anesthesiologist
Department of Anaesthesia and Critical Care
Kenyatta National Hospital, Nairobi
Email: nancy.okonu@yahoo.com

Dr. Caroline M. Mwangi
Cardiac Anaesthetist, Consultant Anesthesiologist and Lecturer
Department of Anaesthesia and Critical Care
University of Nairobi
Email: carlomwa@yahoo.com

Or

The Secretary: KNH/UoN Ethics and Research Committee
Tel: 2726300 Ext:44102

Appendix II: Parental Consent and Study Explanation (Kiswahili Version)

Kichwa cha Utafiti: "The Association between Preoperative Fasting, Blood Glucose Concentration and Blood Ketone Level in Paediatric Patients Undergoing Surgical Procedures at the Kenyatta National Hospital"

Eneo la Utafiti: Hospitali Kuu ya Kitaifa ya Kenyatta na Vituo vya Upasuaji vya Satelaiti

Mpelelezi Mkuu/Uhusiano wa Kitaasisi: Idara ya Anaesthesia, Chuo Kikuu cha Nairobi

Utangulizi:

Ninafanya utafiti kuhusu watoto wanaokwenda kufanyiwa upasuaji katika Hospitali ya Kitaifa ya Kenyatta kuhusu uhusiano kati ya muda wa kufunga kabla ya upasuaji, ukolezi wa glukosi kwenye damu na viwango vya ketone katika damu kwa watoto. Tumeunda fomu hii ya idhini ili itusaidie kukueleza mchakato mzima wa utafiti kwako kama mzazi/mlezi na mtoto ikijumuisha hatari zinazoweza kutokea, madhara, usumbufu au manufaa ambayo utafiti utapata. Unaweza kutuuliza maswali kabla ya kuamua kutoa au kutotoa idhini kwa mtoto wako kuwa sehemu ya utafiti ambao utajumuisha jumla ya watoto 220 kati ya umri wa miaka 0-13.

Kusudi La Utafiti

Utafiti utagundua kama muda wa kufunga kabla ya upasuaji utasababisha mabadiliko yoyote katika mkusanyiko wa glukosi kwenye damu na viwango vya ketone katika damu kwa watoto. Ili kufanya hivyo, nitachukua habari ikijumuisha uzito, jinsia, umri, utambuzi wa upasuaji, hali ya ugonjwa, muda wa mlo wa mwisho na aina ya chakula cha mwisho kilicholiwa. Zaidi ya hayo, shinikizo la damu, kasi ya mapigo ya moyo, kujaa oksijeni, halijoto na kasi ya kupumua vitapimwa kabla ya mtoto wako kulazwa ndani ya chumba cha upasuaji. Mara tu anapokuwa amelala, kiasi kidogo sana cha damu kitachukuliwa kutoka kwenye ncha ya kidole au kidole cha mguu wa mtoto wako kwa kutumia sindano ndogo inayoweza kutupwa kwa uangalifu sana ili kupima kiwango cha sukari kwenye damu na kiwango cha ketone kwenye damu. Taarifa zote zitakazokusanywa zitanakiliwa kwenye fomu maalum kwa kila mtoto anayeshiriki katika utafiti ambayo itachambuliwa na mimi na timu yangu.

Ushiriki

Ikiwa unakubali mtoto wako kuwa mhusika katika utafiti huu, itakuwa ni kwa hiari tu na unaweza kujiondoa wakati wowote. Hutapata gharama yoyote ya ziada kutokana na utafiti huu isipokuwa ile inayohusiana na gharama ya utunzaji katika Hospitali ya Kitaifa ya

Kenyatta. Utafiti hautaingilia, kuathiri au kuchelewesha usimamizi wa mtoto wako na hakutakuwa na manufaa ya kifedha kwa mtoto wako kwa kushiriki.

Hatari za Kushiriki

Kuna hatari ndogo sana zinazohusiana na kushiriki katika utafiti huu na hakuna itakayobadilisha au kubadilisha usimamizi uliopangwa wa mtoto wako.

Usiri

Taarifa zote zitakazokusanywa kuhusu mtoto wako zitakuwa siri kabisa na nitazipata mimi na timu ya watafiti pekee na zitalindwa kila wakati.

Matokeo Ya Utafiti & Usambazaji

Matokeo kutoka kwa utafiti yatashirikiwa na Chuo Kikuu cha Nairobi, Hospitali ya Kitaifa ya Kenyatta na wataalam wengine kupitia majukwaa rasmi yanayofaa.

Ridhaa:

Mimi, _____ mzazi/mlezi/jamaa wa karibu wa _____, mkazi wa _____ napenda kutoa idhini iliyoandikwa ili mtoto wangu ashiriki kwa hiari katika utafiti "uhusiano kati ya muda wa kufunga kabla ya upasuaji, ukolezi wa glukosi katika damu na kiwango cha ketone katika damu kwa wagonjwa wa watoto wanaofanyiwa upasuaji. taratibu katika Hospitali ya Kitaifa ya Kenyatta".

Nimefahamishwa kikamilifu na kuelewa michakato ya utafiti na maswali na wasiwasi wangu wote umeshughulikiwa. Pia ninaelewa kuwa nina haki ya kujiondoa katika utafiti wakati wowote.

Imetiwa saini:_____Tarehe:_____

Tamko La Mchunguzi

Nimeeleza kikamilifu kwa mzazi/mlezi au ndugu wa karibu kuhusu utafiti na nimeshughulikia maswali na hoja zote zilizotolewa.

Imetiwa saini:_____

Tarehe:_____

Ukiwa na maswali au unahitaji Habari Zaidi kuhusu utafiti huu, unaweza kuwasiliana na wafuatao

Mpelelezi Mkuu:

Dk. Gonkarnue Nuahn
Msajili, Idara ya Anesthesia
Chuo Kikuu cha Nairobi, Nairobi, Kenya
Barua pepe: g.nuahn@students.uonbi.ac.ke
Simu ya rununu: 0757161011

Wasimamizi:

Dkt. Nancy N. Okonu
Mtaalamu wa Unusuli wa watoto, Mshauri wa Unuku
Idara ya Anesthesia na Utunzaji Muhimu
Hospitali ya Kitaifa ya Kenyatta, Nairobi
Barua pepe: nancy.okonu@yahoo.com

Dkt. Caroline M. Mwangi
Daktari wa Anaesthetist wa Moyo, Mshauri wa Unuku na Mhadhiri
Idara ya Anesthesia na Utunzaji Muhimu
Chuo Kikuu cha Nairobi
Barua pepe: carlomwa@yahoo.com

Au

Katibu: Kamati ya Maadili na Utafiti ya KNH/UoN
Simu: 2726300 Ext:44102

Appendix III: Child Assent Form for Above 7 Years (English)

(For children 8-13 years)

PROJECT TITLE: **The Association Between Preoperative Fasting Time, Blood Glucose Concentration and Blood Ketone Levels in Paediatric Patients Undergoing Surgical Procedures at the Kenyatta National Hospital**

INVESTIGATOR: **DR. GONKARNUE NUAHN, REGISTRAR, DEPARTMENT OF ANAESTHESIA, UNIVERSITY OF NAIROBI**

We are conducting a research study on whether preoperative fasting time (the amount of time you will not eat any food or drink any fluid before your surgery) will cause any change in the concentration of blood glucose and blood ketones levels in children.

Permission has been granted to undertake this study by the Kenyatta National Hospital-University of Nairobi Ethics and Research Committee (KNH-UoN ERC Protocol No_____). We have also talked to your parents/guardian/next of kin about this research and would like to also ask your permission to be part of the study.

This research study is a way to learn more about how our preoperative fasting practices affect children going for surgical procedures. At least **220** children will be participating in this research study with you.

If you decide that you want to be part of this study, you will be asked give us information about yourself including your age, gender, weight and the type of operation. These questions will be asked before you are taken to the operating theatre either on the same day or the night before. This process usually will take less than 10 minutes.

On the day of your surgery, we will collect additional information from you. We will ask about the time of your last meal and the type of meal. We will also take your vital signs (blood pressure, heart rate, respiration and temperature while you are inside the operating room. Once you are put to sleep, we will take very small amount of blood sample from your fingertip or your toe in a clean and safe manner and measure the glucose and ketone levels with a special machine. The test is associated with small pain or discomfort but you should not feel it because you will already be under anaesthesia.

Not everyone who takes part in this study will benefit. A benefit means something good happens to you. We think the benefits might be seen from what we find in this study which will be used to help us improve how we fast our children going for surgery, make sure they are safe and ensure we detect if anything is wrong with them in a more accurate and faster way.

When we are finished with this study, we will write a report about what was learned. This report will not include your name or that you were in the study.

You do not have to be in this study if you do not want to be. If you decide to stop after we begin, that is okay too. Your parents know everything about the study too.

If you decide you want to be in this study, please sign your name.

I,_____, want to be in this research study.

Signature/Thumb Stamp:_____ Date:_____

Appendix IV: Child Assent Form for Above 7 Years (Kiswahili)

(Kwa watoto wa miaka 8-13)

Kichwa cha Utafiti: "**The Association between Preoperative Fasting, Blood Glucose Concentration and Blood Ketone Level in Paediatric Patients Undergoing Surgical Procedures at the Kenyatta National Hospital"**

Mpelelezi Mkuu: Dkt. Gonkarnue Nuahn , Msajili, Idara ya Anesthesia, Chuo Kikuu cha Nairobi

Tunafanya utafiti kuhusu iwapo muda wa kufunga kabla ya upasuaji (muda ambao hutakula chakula chochote au kunywa maji yoyote kabla ya upasuaji) utasababisha mabadiliko yoyote katika mkusanyiko wa glukosi kwenye damu na viwango vya ketoni za damu kwa watoto.

Ruhusa imetolewa kufanya utafiti huu na Hospitali ya Kitaifa ya Kenyatta-Kamati ya Maadili na Utafiti ya Chuo Kikuu cha Nairobi (KNH-UoN ERC Protocol No_____).

Pia tumezungumza na wazazi/mlezi/jamaa wako kuhusu utafiti huu na tungependa pia kukuomba ruhusa ya kuwa sehemu ya utafiti.

Utafiti huu ni njia ya kujifunza zaidi kuhusu jinsi desturi zetu za kufunga kabla ya upasuaji zinavyoathiri watoto wanaokwenda kufanyiwa upasuaji. Angalau watoto 220 watashiriki nawe katika utafiti huu.

Ukiamua kuwa ungependa kuwa sehemu ya utafiti huu, utaulizwa utupe maelezo kukuhusu ikiwa ni pamoja na umri wako, jinsia, uzito na aina ya operesheni. Maswali haya yataulizwa kabla ya kupelekwa kwenye chumba cha upasuaji ama siku ile ile au usiku uliotangulia. Utaratibu huu kwa kawaida utachukua chini ya dakika 10.

Siku ya upasuaji wako, tutakusanya maelezo ya ziada kutoka kwako. Tutakuuliza kuhusu muda wa mlo wako wa mwisho na aina ya chakula. Pia tutachukua dalili zako muhimu (shinikizo la damu, mapigo ya moyo, upumuaji na halijoto ukiwa ndani ya chumba cha upasuaji. Mara tu unapolazwa, tutachukua sampuli ndogo sana ya damu kutoka kwenye ncha ya kidole chako au kidole chako cha mguu kwa kusafisha. na namna salama na kupima viwango vya glukosi na ketone kwa mashine maalum.Kipimo hicho kinahusishwa na maumivu madogo au usumbufu lakini hupaswi kuhisi kwa sababu tayari utakuwa chini ya anesthesia.

Si kila mtu atakayeshiriki katika utafiti huu atafaidika. Faida inamaanisha kitu kizuri kinatokea kwako. Tunafikiri manufaa yanaweza kuonekana kutokana na yale tunayopata katika utafiti huu ambayo yatatumika kutusaidia kuboresha jinsi tunavyowafunga watoto wetu kufanyiwa upasuaji, kuhakikisha kwamba wako salama na kuhakikisha kuwa

tunatambua kama kuna jambo lolote lisilo sawa nao kwa usahihi zaidi. na njia ya haraka zaidi.

Tukimaliza na somo hili, tutaandika ripoti kuhusu kile tulichojifunza. Ripoti hii haitajumuisha jina lako au kwamba ulikuwa kwenye utafiti. Si lazima uwe katika utafiti huu ikiwa hutaki kuwa. Ukiamua kuacha baada ya sisi kuanza, hiyo ni sawa pia. Wazazi wako wanajua kila kitu kuhusu utafiti pia. Ukiamua ungependa kuwa katika utafiti huu, tafadhali saini jina lako.

Mimi,_____, nataka kuwa katika utafiti huu.

Sahihi/Muhuri wa Kidole:_____ Tarehe:_____

Appendix V: Data Collection Tool

Code: ____

Ward of Admission_____

Demographic Data:

Age: _____yrs_____months_____weeks_____days

Weight:_____kg

Gender: M ☐ F ☐

Clinical Data:

Diagnosis:_____

Urgency of Surgery: elective ☐ emergency ☐

Comobidity:_____

Type of Last Meal: clear fluids ☐ breast milk ☐ other milk ☐ solids ☐

Time of Last Meal: _____ AM/PM Time of Sample Collection:_____ AM/PM

Measurements of Vital Signs at Induction of Anaesthesia:

Blood Pressure:_____mmHg Heart Rate_____b/min Resp:_____br/min

Temp:____C

Blood glucose:_____mmol/L

Blood ketone:_____mmol/L

Total Fasting Time: _____Hrs_____Min

Appendix VI: Summary of International Fasting Guidelines

Country/year	Fasting requirements at induction	comments
American Society of Anesthesiologists, 2017	■ 2 hours clear liquids, excluding alcohol ■ 4 hours breast milk ■ 6 hours nonhuman milk, formula, light meal ■ 8 hours or more for fatty meal, fried food, meat	Healthy patients, not in labor, elective surgery Light meal defined as toast or cereal with clear liquid
European Society of Anesthesiology and Intensive Care	■ 1 hour clear liquids 3 hours breast milk 4 hours formula or nonhuman milk, light breakfast (weak recommendations) 6 hours other solid food	Encourage oral fluid up until fasting time
Association of Anesthetists in Great Britain and Ireland	■ 2 hours clear liquids ■ 4 hours breast milk ■ 6 hours solid food, formula and cow's milk	Gum chewing treated as clear fluid
Australian and New Zealand College of Anesthetists	■ 1 hour clear fluid (≤3 mL/kg/hour) for infants and children ■ 2 hours clear liquids adults ■ 3 hours breast milk for infants <6 months ■ 4 hours formula for infants <6 months ■ 6 hours breast milk, formula, limited solid food for children >6 months and adults	Up to 400 mL of clear liquid up to 2 hours prior to induction for adults is likely safe
Scandinavian Society of Anaesthesiology and Intensive Care Medicine	■ 2 hours clear liquids ■ 4 hours breast milk and infant formula ■ 6 hours solid food and cows milk ■ 2 hours chewing gum and any tobacco	2 hours for preoperative carbohydrate drinks intended

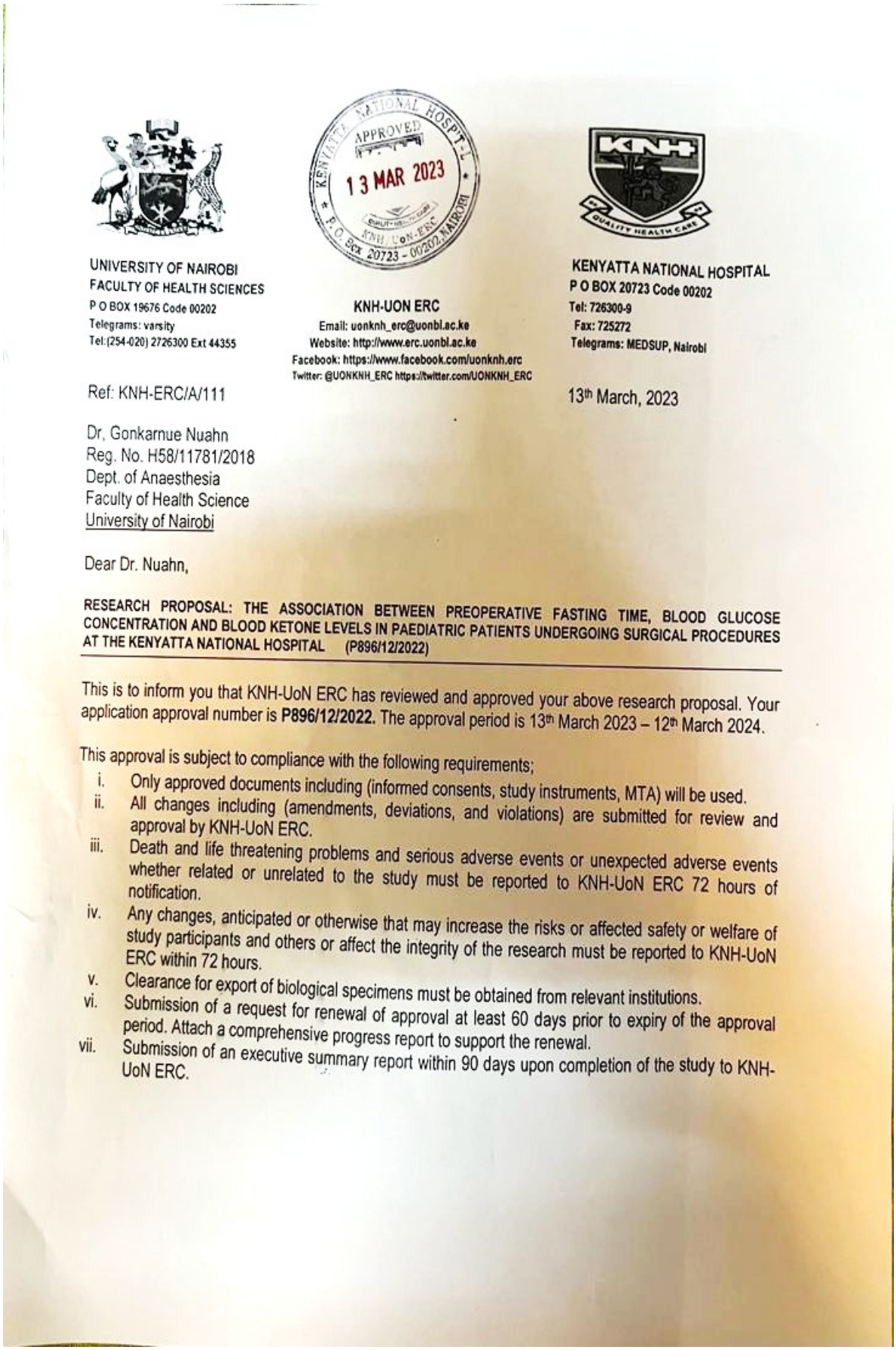
■	product Up to 1 hour prior to induction, 150 mL of water	for preoperative nutrition
Joint statement from ■ Association of Paediatric Anaesthetists of Great Britain ■ and Ireland, European Society for Paediatric Anaesthesiology, L'Association Des Anesthésistes-Réanimateurs Pédiatriques d'Expression Française	1 hour clear liquids for children up to 16 years of age	Encourage intake of clear liquids
Canadian Pediatric Anesthesia ■ Society	1-hour clear liquids for children ■	Encourage intake of clear liquids
The Society for Paediatric ■ Anaesthesia of New Zealand and Australia	1-hour clear liquids for children ■	Encourage intake of clear liquids

Appendix VII: American Society of Anesthesiologists Physical Status Classification

ASA CLASS	DEFINITION	EXAMPLES INCLUDING BUT NOT LIMITED TO:
ASA I	A normal healthy patient	normal history & physical exam
ASA II	A patient with mild systemic disease without restricted function	Well controlled hypertension, diabetes mellitus, well controlled asthma, etc
ASA III	A patient with severe systemic disease with restricted functions	Poorly controlled asthma, diabetes, or hypertension, COPD, morbid obesity, etc
ASA IV	A patient with severe systemic disease that is a	recent MI, CVA, TIA, CAD/stents in less than 3

	constant threat to life	months, severe cardiac disease, sepsis, DIC, ESRD without regular dialysis
ASA V	A moribund patient who is not expected to survive without the operation	Ruptured aneurysm, massive trauma, intracranial bleed with mass effect, multiple organ/system dysfunction
ASA VI	A declared brain-dead patient whose organs are being removed for donor purposes	

Appendix VIII: KNH/UoN-ERC Letter of Approval



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KENYATTA NATIONAL HOSPITAL
APPROVED
13 MAR 2023
P.O. BOX 20723 - 00202, NAIROBI

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Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/111

13th March, 2023

Dr. Gonkarnue Nuahn
Reg. No. H58/11781/2018
Dept. of Anaesthesia
Faculty of Health Science
University of Nairobi

Dear Dr. Nuahn,

RESEARCH PROPOSAL: THE ASSOCIATION BETWEEN PREOPERATIVE FASTING TIME, BLOOD GLUCOSE CONCENTRATION AND BLOOD KETONE LEVELS IN PAEDIATRIC PATIENTS UNDERGOING SURGICAL PROCEDURES AT THE KENYATTA NATIONAL HOSPITAL (P896/12/2022)

This is to inform you that KNH-UoN ERC has reviewed and approved your above research proposal. Your application approval number is **P896/12/2022.** The approval period is 13th March 2023 – 12th March 2024.

This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, MTA) will be used.
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by KNH-UoN ERC.
iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to KNH-UoN ERC 72 hours of notification.
iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH-UoN ERC within 72 hours.
v. Clearance for export of biological specimens must be obtained from relevant institutions.
vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal.
vii. Submission of an executive summary report within 90 days upon completion of the study to KNH-UoN ERC.

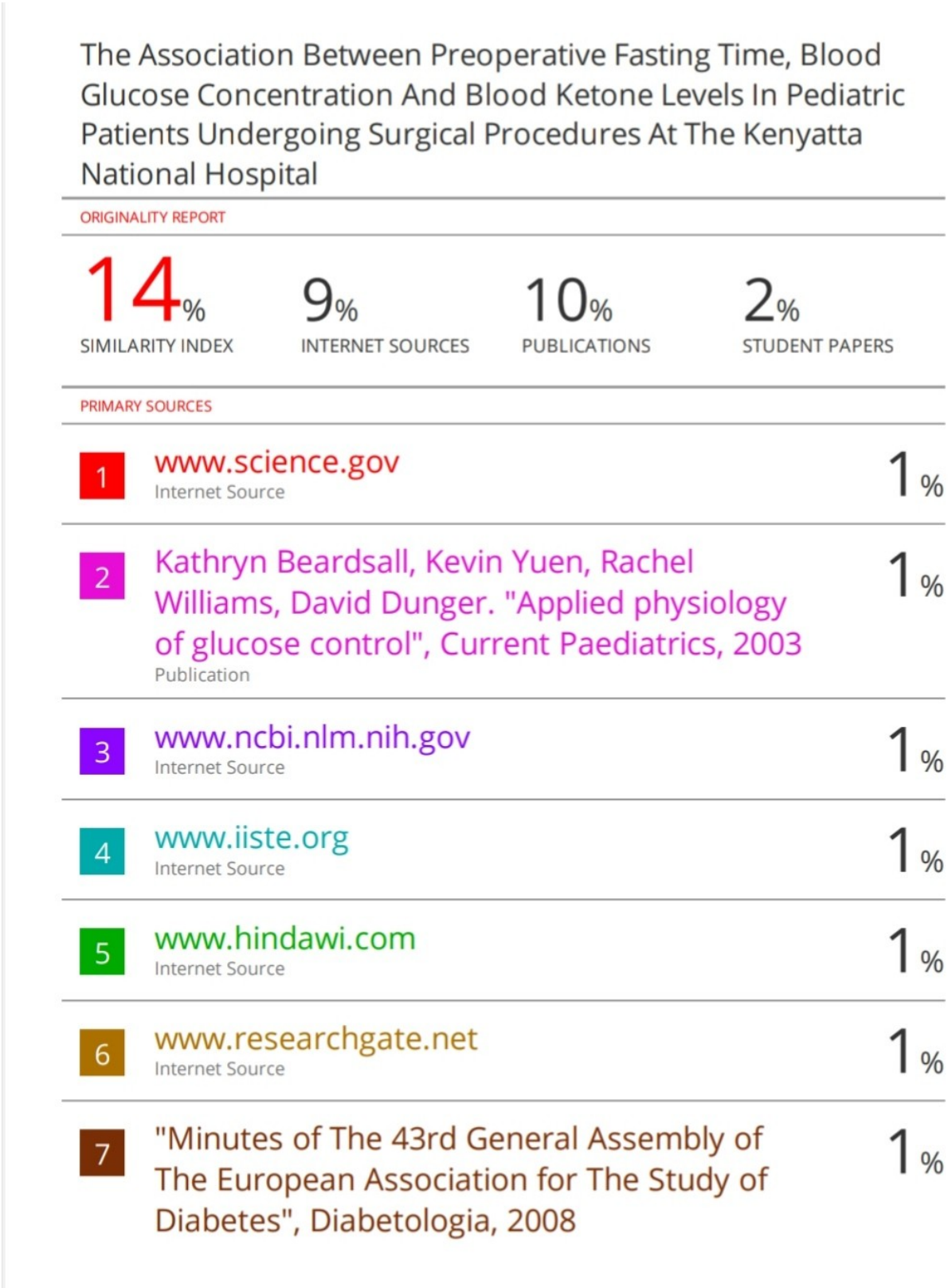
Prior to commencing your study, you will be expected to obtain a research license from National Commission for Science, Technology and Innovation (NACOSTI) https://research-portal.nacosti.go.ke and also obtain other clearances needed.

Yours sincerely,

DR. BEATRICE K.M. AMUGUNE
SECRETARY, KNH-UoN ERC

c.c. The Dean, Faculty of Health Sciences, UoN
The Senior Director, CS, KNH
The Assistant Director, Health Information Dept., KNH
The Chairperson, KNH- UoN ERC
The chair, Dept. of Anaesthesia UoN
Supervisors: Dr. Nancy N Okonu, Dept. of Anaesthesia & Critical Care, KNH
Dr. Caroline Muthoni Mwangi, Dept of Anaesthesia, UoN

Appendix IX: Plagiarism Certificate



The Association Between Preoperative Fasting Time, Blood Glucose Concentration And Blood Ketone Levels In Pediatric Patients Undergoing Surgical Procedures At The Kenyatta National Hospital

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