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TRIGLYCERIDE-GLUCOSE INDEX MODEL AS A TOOL FOR MONITORING GLUCOSE LEVEL AND ASSESSING TREATMENT FOR DIABETIC PATIENTS WITH INSULINAEMIA

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ABSTRACT
This examination investigated the triglyceride-glucose (TYG) model of monitoring glucose level and assessing treatment in human diabetic subjects. The assessment solidified the human diabetic subjects in the evaluation of TYG model, and took the blood analytes to screen for diabetes. 120 male and female human subjects containing forty subjects each for control, pre-diabetics, and diabetics facilitated for age, sex, height, weight and BMI. Twenty each of the three sets of human subjects were males and females independently. Every illustration of blood serum and plasma was explored using Randox and Accubind packs and an autoanalyser to test for various biochemical and hematological limits. The overall results revealed a colossal differentiation ($p \leq 0.05$) in the limits except for that of Na^+. The 500mg/kg body weight part of the concentrate was ideal and TYG potential gains of 3.69±0.02, 3.90±0.02, and 4.04±0.02 for the three sets independently. This assessment revealed that TYG is good for the management of diabetes.

KEYWORDS: diabetes, pre-diabetics, analytes, TYG model.

Contributions to Knowledge
The research used human diabetic subjects in the evaluation of the TYG model and compared the blood analytes of non-diabetics, pre-diabetics, and diabetics in order to monitor the onset of diabetes and proffer possible solutions to enhance early detection and manage diabetes.

INTRODUCTION
Insulin is usually released from the pancreatic ß-cells, directly stimulating glucose release into peripheral insulin target tissues as well as suppressing hepatic glucose output (HGO). Interference with any of these actions of insulin will tend towards increase in blood glucose concentration, a condition commonly termed hyperglycemia. Thus, in optimal secretion and action, insulin is desired to enthrone normal plasma glucose concentration, normoglycemia. (Greeve, 2005), but for deviations that may lead to reduced or increased secretion of the hormone. Commonly, insulin can either be sensitive or resistant to available plasma glucose.

Insulin resistance is the reduced ability of insulin to exert its biological effects on target tissues, such as; adipose tissue, skeletal muscle and liver. Physiologically, it is an inappropriately high level of insulin as against available glucose (Lee *et al.*, 2007).

Over the years, several assessment models for insulin have been developed, with varying outcomes, which also depicts either their benefits or disadvantages. There are three commonly employed assessment models (Homeostasis model assessment of insulin resistance (HOMA-IR) index, Triglyceride and glucose (TYG) index, and Triglyceride/high density lipoprotein (TG-HDL) cholesterol ratio) of insulin resistance in diabetics. The TyG index is novel, but demonstrates high sensitivity and specificity in identifying metabolic syndrome. However, the TyG index is reported to be associated with carotid atherosclerosis, coronary artery calcification and high risk of cerebrovascular disease.

Some clinical conditions are associated with insulin resistance. This includes high levels of triglyceride (TG), increased waist circumference (visceral adiposity), hypertension, hyperglycaemia and dyslipidaemia (Lee *et al.*, 2007; Greeve, 2005). Others are hypercoaguable state and increased inflammatory cytokine levels (Marckmann, 2000). These are also features of metabolic syndrome, a common condition associated with increased cardiovascular risk and increased risk of

diabetes (Vega, 2001). Although the link between obesity and insulin resistance is well established, insulin resistance may be present in non-obese and non-diabetic individuals, in addition to other components of metabolic syndrome (Ginsberg, 2000; Kahn & Flier, 2000). Insulin resistance is further associated with the development of metabolic syndrome (Kahn *et al.*, 2006), a cluster of cardiometabolic risk factors that promote development of cardiovascular disease and type 2 diabetes (Malik *et al*., 2004; Ford, 2005). The health concerns linked to insulin resistance are enumerated to include severe hyperglycemia and hypoglycemia, heart attacks, strokes, kidney disease, eye problem, and cancer. But the prompting symptoms of the condition extreme thirst or hunger, feeling hungry even after a meal and increased or frequent urination.

Insulin resistance (IR) in humans is proven to be consistent with conditions like non-insulin dependent diabetes mellitus (NIDDM) and dyslipidemia. It is broadly considered a major risk factor in the etiology of type 2 diabetes mellitus (Bray, 2004). The condition requires interventions to postpone the development of NIDDM and its complications. It is commonly associated with excess release of insulin to lower plasma glucose levels, hyperinsulinaemia. Hyperinsulinemia accounts for reduced peripheral insulin sensitivity (Khan, 2003). Several risk factors, such as obesity, physical inactivity, body fat distribution, age and hyperinsulinemia, may also be indicative of insulin resistance. Insulin resistance is a predictor for the development of type 2 diabetes mellitus, obesity, septicemia, polycystic ovary syndrome and excess glucocorticoids (Buse, 2006). It is thus, pertinent to investigate insulin resistance in the pre-disease stage, when treatment may be helpful than in overt disease (Boden, 2001).

Insulin resistance is also associated with elevated blood pressure (BP) and common in patients with type 2 diabetes (T2D), which reflects on the vasculature and kidney (Ferrannini & Cushman, 2012). Conditions such as type 2 DM can be treated with herbs, but is fraught with side effects. Thus, synthetic agents are usually employed and reported to be effective. Dexamethasone (Dex) is one of such agents, but also has its shortcomings. Dex increases triglyceride levels, leading to imbalance in lipid metabolism, attendant hyperlipidemia and increased plasma glucose levels, hyperglycemia (Mahendran *et al.*, 2001).

Diabetes is a metabolic condition occasioned by inability of the body inability to produce or utilize insulin, with a potential to drastically decrease the quality of human life. The World Health Organization (WHO) (1996) posits that about 150 million people suffer from diabetes mellitus globally, with the number likely to triple by the year 2025 to about 57 million, while India has the highest number. However, the International Diabetes Federation (IDF) (2000) projected the global prevalence as 151 million by 2000, 194 million by 2003, 246 million by 2006, 285 million by 2009, 366 million by 2011, 382 million by 2013 and 415 million by 2015. Nigeria is reported to have the most incidence and prevalence of the disease in Africa, at about 4 million and 4.99% respectively (IDF, 2015), with the type 2 subset accounting for approximately 95% (IDF, 2013; ADA, 2014). This subset (type 2) also has multifactorial etiology; including genetics and environment (Schaalan *et al*., 2009; Willett, 2002). The global prevalence of diabetes and impaired glucose tolerance in adults has increased over recent decades (Ogurtsova *et al.*, 2017; Guariguata *et al.*, 2014; Whiting *et al*., 2011; Shaw *et al*., 2010). The pace of change in diabetes prevalence in many countries is attributed to rapid urbanization and sudden changes towards sedentary lifestyle (Blas *et al.*, 2010).

Routine fasting blood sugar test investigates glycaemic state, but is dependent on diurnal fluctuation. Glycated haemoglobin (HbA1c) test points to previous FBS level (past 1 to 3 months) and are relevant for diagnosing diabetes. High HbA1c indicates high FBS level in the past 3 months and likelihood of developing long-term complications (World Health Organization (WHO), 2011). It is important to detect the level of glucose in individuals, but it is more important if such tests can predict predisposition to disease conditions, which may serve as a foundation to prevent such ailments and the complications associated with them. Current research focuses on markers that predict diseases, such as, diabetes mellitus and CVD (Wild *et al.*, 2004). Such researches can aid the control and delay the onset of diseases, while developing techniques that will be employed in its use. The purpose is to provide baseline data that will aid the assessment of insulin resistance among individuals for physicians. However, such techniques are rarely employed in developing and resource-constrained climes, but have continuously been advocated for. The TYG index is among such techniques observed to be useful for both normal and diabetic patients, to determine the glucose levels, which is the underlying nutrient in some metabolic conditions. The role of some naturally-occurring herbs in controlling blood glucose level and development of insulin resistance, such as ginger and aloe vera are also investigated, using the TYG index technique, since these herbs, which have long been used as drink and spices (Tajkarimi *et al.*, 2010), are thought to have medicinal roles in regulating blood sugar.

Guerrero-Romero *et al.*, (2010) and Simental-Mendía *et al.*, (2008) proposed the formula to evaluate IR, known as TYG index in 2010 and have been widely accepted and employed. Its role in evaluating triglycerides and glucose is valuable due to relationship between plasma triglycerides and glucose in the etiology of T2DM (Freeman *et al*., 2001; Dotevall *et al.*, 2004). The both nutrients (triglyceride and glucose) also play a role in the development of CVD, thus, the index serves to predict a

CVD risk (Shaye *et al.*, 2012). TyG index is a novel marker with demonstrated high sensitivity and specificity in identifying metabolic syndrome (Angoorani *et al.*, 2018). However, it comes with some demerits, which include carotid atherosclerosis, coronary artery calcification and high risk of CVD (Kim *et al.*, 2017; Sánchez-Íñigo *et al*., 2016; Irace *et al.*, 2013), but shows improved efficiency compared to previous markers (Du *et al*., 2014; Guerrero-Romero *et al.*, 2010; Simental-Mendía *et al*., 2008).

METHODOLOGY

The study area was Choba and Aluu, with the centers being University of Port Harcourt and University of Port Harcourt Teaching Hospital (UPTH). They are in Obio/Akpor and Ikwerre Local Government Areas of Rivers State, Nigeria. Cannula (catheter), cotton wool, methylated spirit, micropipettes, plain bottles, sample containers, syringes and needles, test-tubes, test-tube racks, reagents and tourniquet were some materials used. Extracts used were from aloe vera, ginger and cinnamon. The participants were sourced from UPTH (individuals coming for monitoring of their glucose level, insulin resistance and TyG over a period of 2 months. Each individual was provided an informed consent form, while willing individuals donated an aliquot (5ml) of their blood samples after their grouping, and the Ethical approvals for the study were obtained from the Ethical Unit of the School of Post Graduate studies, University of Port Harcourt and the Legal Unit of the UPTH. The respondents were grouped majorly into two: control GROUP A (control) and test Groups B (prediabetics) and C (diabetics) of 40 each. Inclusion criterion was subjects aged 36 to 76 years, while the exclusion criterion was co-infection and other metabolic disorders.

Plant samples (aloe vera leaves and ginger rhizomes) were purchased from markets in Port Harcourt City and Obio/Akpor Local Government Areas respectively of Rivers State, Nigeria. Also, the minimum sample size was calculated employing the formula shown by Anderson *et al.* (1991): $N = Z^2 (pq) / e^2$, where N is minimum sample size, Z is 1.96 at 95% confidence limits, so that $z^2 = 3.8416$, p is prevalence of increased normal and diabetic subjects' percentage average, q = 1-p (6.80% as the prevalence of increased normal subjects and 10.20% as the prevalence of increased diabetic subjects) giving ((6.80 + 10.20)/2)% = (17.00/2)% = 8.50% and 8.50% as the prevalence of increased mean of normal and diabetic subjects. p is 8.50% = 0.0850, q is 1-p = 1-0.0850 = 0.9150 and e is error margin tolerated at 5% = 0.05 ($e^2 = 0.0025$).

N = ((3.8416(0.0850 x 0.9150))/0.0025 = 119.51 = approximately 120.

RESULTS

Table 1: Bio-data of human subjects for the non-diabetic control, pre-diabetic, and diabetic groups.

GROUP	SEX		AGE (years)	HEIGHT (cm)	WEIGHT (kg)	SYSTOLIC (mmHg)	DIASTOLIC (mmHg)	BMI
	F	M						
NON-DIABETIC	20±0.03	20±0.04	50.70±1.16^{c}	176.20±1.25^{b}	70.76±0.89^{c}	110.12±1.59	71.77±0.89	22.88±0.43^{c}
PRE-DIABETIC	21±0.13	19±0.11	54.87±1.67^{a}	170.82±1.09^{c}	72.32±1.24^{c}	111.52±1.96	74.07±0.94	25.10±0.43^{a}
DIABETIC	20±0.00	20±0.00	56.12±1.62^{a}	173.47±0.93^{b}	76.27±2.13^{ab}	119.77±1.96	75.70±0.88	25.34±0.10^{a}

The height of the non-diabetic and diabetic groups was not significantly different (176.20±1.25cm and 173.47±0.93cm), but the height of the pre-diabetics (170.82±1.09cm) was significantly different ($p<0.05$) from the other 2 groups.

The weight of the pre-diabetics was higher but not statistically different from that of the non-diabetics, the weight of the diabetics (76.27±2.13kg) was statistically higher ($p<0.05$) than that of the non-diabetics (70.77±0.89kg) and pre-diabetics (72.32±1.24kg). Analysis of the BMI showed that the BMI was not statistically different ($p<0.05$) in the pre-diabetics (25.10±0.43) and diabetics (25.34±0.10), however, both groups were significantly higher than that for the non-diabetics (22.88±0.43). Both the systolic and diastolic pressure of the diabetics (119/75 mmHg) were significantly ($p<0.05$) higher than that of the non-diabetics (110/72 mmHg). Systolic pressure of the diabetics was also statistically higher ($p<0.05$) than that of the pre-diabetics but the diastolic pressure was not statistically different ($p>0.05$), 119/75 mmHg and 112/74 mmHg respectively.

Table 2: Glucose, HbA1c (Glycemic indexes) and Insulin of human subjects.

GROUP	Glucose mmol/l	HbA1c mmol/l	Insulin mIU/L
NON-DIABETIC	4.49±0.08^{bc}	4.75±0.05^{bc}	4.77±0.19^{bc}
PRE-DIABETIC	6.00±0.11^{ac}	5.73±0.08^{ac}	8.48±0.59^{a}
DIABETIC	10.84±0.96^{a}	9.74±0.47^{a}	7.13±0.73^{ab}

The glucose and HbA1c showed significantly increasing trend with values of 4.49±0.08 mmol/l, 6.00±0.11 mmol/l, and 10.84±0.96 mmol/l for glucose; and 4.75±0.05 mmol/l, 5.73±0.08 mmol/l, and 9.74±0.47 mmol/l for HbA1c, for the non-diabetics, pre-diabetics and diabetics respectively. All values were significantly higher ($p<0.05$) across the groups for both glucose and HbA1c. Insulin levels were also significantly higher

(p<0.05) across the groups but did not show the same linearity having the highest value with the pre-diabetic group. The levels were 4.77±0.19 mIU/L, 8.48±0.59 mIU/L, and 7.13±0.73 mIU/L for the non-diabetics, pre-diabetics and diabetics respectively.

Table 3: Triglyceride-Glucose index in non-diabetic, pre-diabetic and diabetic groups.

GROUP	TRIGLYCERIDE-GLUCOSE INDEX
NON- DIABETIC	3.69 ± 0.02^{c}
PRE-DIABETIC	3.90 ± 0.02^{ac}
DIABETIC	4.04 ± 0.06^{ab}

Table 3 above reveals an increasing trend in the TYG index across the groups. The values were linear showing 3.69±0.02 for the non-diabetics, 3.90±0.02 for the pre-diabetics, and 4.04±0.02 for the diabetics. The values of diabetics and pre-diabetics were significantly higher than that of the non-diabetics.

Table 4: RBC, PLT, WBC counts and their components.

GROUP	RBC ($\times10^6$ cells/cmm)	Hb (g/dL)	PCV (%)	PLT ($\times10^9$/L)	WBC ($\times10^9$/L)	NEU ($\times10^9$/L)	LYMP ($\times10^9$/L)	MONO ($\times10^9$/L)	EOS ($\times10^9$/L)	BAS ($\times10^9$/L)
NON-DIABETIC	4.29 ± 0.07^{c}	13.98±0.51	42.30±0.75	186.95 ± 6.04^{c}	5.52±0.13	25.20 ± 0.59^{c}	64.55 ± 0.66^{c}	6.10 ± 0.20^{c}	3.25 ± 0.11^{c}	0.15±0.07
PRE-DIABETIC	4.38 ± 1.05^{c}	14.03±0.17	43.70±0.53	206.70 ± 8.72^{ac}	5.60±0.20	26.37 ± 1.48^{c}	65.42 ± 1.70^{c}	6.32 ± 0.28^{ac}	3.62 ± 0.16^{a}	0.15±0.05
DIABETIC	4.90 ± 0.11^{ab}	14.12±0.29	43.92±0.84	229.97 ± 11.21^{ab}	5.68±0.37	29.47 ± 8.63^{ab}	68.52 ± 2.35^{ab}	6.82 ± 0.46^{b}	3.80 ± 0.15^{a}	0.10±0.04

Table 4 above shows that RBC was significantly higher (p<0.05) in the diabetics, with values of 4.29±0.07 mL, 4.38±1.05 mL, and 4.90±0.11 mL for non-diabetic, pre-diabetic and diabetics respectively. Platelet (PLT) count was significantly increased (p<0.05) in the pre-diabetic and diabetic groups showing values of 186.95±6.04 mL, 206.70±8.72 mL, and 229.97±11.21 mL respectively for the non-diabetics, pre-diabetics and diabetics. Hb and PCV were not statistically different (p>0.05) across the groups though non-diabetic patients had slightly lower Hb and PCV than other groups. WBC count was slightly increased in the pre-diabetic and diabetic groups although the increase was not statistically significant. Neutrophil count of the diabetics was statistically higher (p<0.05) than that of non-diabetics and pre-diabetics with values of 25.20±0.59 cells/µL, 26.37±1.48 cells/µL, and 29.47±8.63 cells/µL for the non-diabetics, pre-diabetics and diabetics respectively. Lymphocytes counts also increased progressively from the non-diabetic to the pre-diabetics and diabetics but this increase was only significant (p<0.05) in the diabetic group. Eosinophil count increased progressively across the groups with the increase being significant (p<0.05) in the diabetic group relative to the non-diabetic and pre diabetic groups as shown in the Table 4.6 below. Monocyte count was also significantly different across the groups with values of 6.10±0.20 cells/µL, 6.32±0.28 cells/µL, and 6.82±0.46 cells/µL for non-diabetic, pre-diabetics and diabetics respectively. Basophil count on the other hand, was basically the same across all groups as represented in the table.

DISCUSSION

There is a correlation between diabetes and the body mass index (BMI) of subjects. In fact, obesity is believed to account for 80 to 85% of the risk of developing type 2 diabetes while recent research suggests that obese people are about 80 times more likely to develop type 2 diabetes than those with a BMI of <22 (McGill, 2005). Thus young, lean, physically fit individuals are likely to be highly insulin sensitive, while obese subjects with type 2 diabetes will have poor insulin sensitivity (Greeve, 2005). This is supported by this study. The average body weight of the human subjects showed a trend of increase from the non-diabetic, pre-diabetic to the diabetic subjects. The BMI of the pre-diabetic and diabetic subjects were also significantly higher than that of the non-diabetic subjects. There is also a correlation between diabetes and high blood pressure (BP) as the BP increased significantly across the normal, pre-diabetic and diabetic subjects in a similar order. Low insulin as well as unresponsive insulin promotes gluconeogenesis, glycogenolysis and glycolysis.

There are a number of factors which can contribute to becoming obese such as eating a high calorie diet (high fat diet), not getting enough physical exercise, genetics, medical conditions and being on medications. Loss of body weight also improves blood glucose levels (McGill, 2005) and allows people with type 2 diabetes to come off or avoid developing insulin resistance. Obesity triggers changes to the metabolism of the body. These changes cause adipose tissue to release fat molecules into the blood which can affect insulin responsiveness in cells and lead to reduced insulin sensitivity. Obesity causes pre-diabetes, a condition associated with type 2 diabetes (Bray, 2004).

Triglyceride-Glucose index shows positive correlation with another index for glucose investigation, homeostatic model of assessing insulin resistance (HOMA-IR) (Locateli *et al.*, 2019). In this work, TYG index followed a pattern, being significantly increased in pre-diabetic and diabetic subjects. There is decreased glycaemic state as indicated by the Glucose and HbA1c levels and was lowest in the diabetic subjects, just as insulin resistance significantly increases as disease progresses (Ogbonna *et al.*, 2019; Chutia *et al.*, 2018). This study is in agreement

with this, as we found increased Glycaemia as represented by the glucose and HbA1c concentrations.
Analysis of haematological parameters in the subjects showed alterations in haematological indices in the diabetic state. Diabetes is characterized by hyperglycaemia, dyslipidemia, hypertension and impaired hematological indices. Some hematological changes affecting the RBCs, WBCs and coagulation factors are observed to be directly associated with DM (Biadgo *et al.*, 2016). Other hematological abnormalities reported in the DM patients include RBCs, WBCs and platelet dysfunction (Gkrania-Klotsas *et al.*, 2010). In this study, PCV, Hb and RBC were all higher in the pre-diabetic and diabetic human subjects relative to the controls, though the difference was not significant for PCV and Hb. RBC was however significantly higher in the diabetic subjects. Platelet count and WBC count and its components were also found to be elevated in the pre-diabetic and diabetic subjects. This is in agreement with findings reported in other studies and might be the indirect features of insulin resistance syndrome, since it is associated with increased WBC and RBC counts, and increased levels of Hb (Biadgo *et al.*, 2016). Increase in WBC indices in the diabetic group compared with the control group may also be due to increased oxidative stress triggered by the high levels of hyperglycemia in the diabetic patients. In contrast, other studies reported decrease in RBC count, Hb and PCV levels (Ezenwaka *et al.*, 2008). This might be expected in diabetes of long duration as chronic hyperglycaemia and glycation of red blood cell membrane proteins will lead to accelerated aging of RBCs.

Summary/Conclusion

Insulin resistance is generally accepted as a major risk factor in the etiology of type 2 diabetes mellitus (Bray, 2004). Several risk factors, like obesity, physical inactivity, body fat distribution, age and hyperinsulinemia are considered as markers of insulin resistance. Insulin resistance is a predictor for the development of Type 2 diabetes mellitus even in individuals with normal glucose tolerance. Therefore, it is important to recognize insulin resistance in pre-disease stage when therapeutic intervention will be more successful than in manifest disease (Boden, 2001).

This study aimed at proposing a new system where normal and diabetic subjects can assess FBG, insulin resistance level and their TyG, in order to predict and monitor or control DM best.

The human model was designed and used to assay various biochemical and haematological parameters and the findings largely corroborated previous studies with few exceptions.

The human model designed and used to assay various biochemical and haematological parameters, using the TYG index, largely corroborated with previous studies. Dyslipidaemia and hyperinsulinaemia was seen in sampled subjects. Risk factors, such as obesity, physical inactivity, body fat distribution, age and hyperinsulinemia may be considered markers of diabetes. It is recommended that larger population should be used this research and should be conducted in various geographical locations as variations in different locations affect the genetic factor and limit the generalization of research findings.

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