# Assessment of Insulin Resistance in Normal and Diabetic Subjects Using Homeostatic Model and Other Indices

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***Abstract:*** **This study assessed insulin resistance in normal and diabetic human subjects using homeostatic model (HOMAIR).Bio-data were used to investigate the association between Insulin resistance and diabetes, and to compare the effect of these pathological conditions on human subjects. Investigation of Insulin, HbA1c, Glucose, TSH, fT3, fT4 on the normal, pre-diabetic and diabetic human subjects alongside Haematological indices were carried out.One hundred and twenty human subjects comprising forty subjects each for control, pre-diabetics, and diabetics (three sets) matched for age, sex, height, weight, and blood pressure were recruited into the study based upon specified criteria. Twenty each for the three sets of human subjects were males and females respectively. Each sample of blood serum and plasma was analyzed using Randox kits to test for various biochemical and haematological parameters. Compared with the human control, the mean values of the parameters were significantly different ($p<0.05$) from each other with few exceptions an increase in HOMAIR was shown with values of 0.94±0.04, 2.28±0.17, and 3.25±0.44 for the three sets respectively. Conclusively, the assessment of insulin resistance studied using the models proved that insulin resistance can be managed when appropriate lifestyle is adopted.**

***Keywords:*** **Insulin resistance, Diabetes, Homeostatic model, HOMA-IR, Hematology, Hormone**

## I. INTRODUCTION

Current trends in research are in favour of markers that are predictive of diabetes mellitus (DM). Such measures would detect DM at the pre-diabetic state. It would mean then, that once any of such markers begin to rise, it is an indication that such a person involved, is at risk of diabetes or any cardiovascular disorder (CVD) (Wild *et al*., 2004). Therefore, if such markers could be found and controlled, the onset of DM could be delayed or even starved off. One common marker is insulin, the hormone responsible for regulation of blood glucose.

The Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), measures insulin resistance. The calculation marks for both the presence and extent of any insulin resistance and is an excellent way of revealing the dynamics between an individual's baseline (fasting) blood sugar and the responsive hormone insulin. Metabolic health lies in the space between the hormone insulin and your glucose sensitivity (Vogeser, 2007; Maurer, 2014). Low HOMA-IR means that you are sensitive to insulin. A small amount of the hormone is doing the job of regulating your blood glucose in good balance. The higher the HOMA-IR, the more resistant you are to the message of insulin.

Uncorrected high insulin will usually, over time result in insulin resistance. Development and increase in insulin resistance, shows that a person is heading for diabetes; when insulin can act no more, the glucose level then rises rapidly, and diabetes is the consequent result of these metabolic changes (Vogeser, 2007). Investigation of insulin homeostasis has become, therefore, very important in DM and this is what is being advocated in developing countries such as Nigeria.

Investigation of Insulin, HbA1c, Glucose, Lipid Profile, Thyroid Stimulating Hormone (TSH), Free Triiodothyronine (fT3), Free Thyroxine (fT4), Full Blood Count (FBC), and assessment of HOMA-IR, Triglyceride/High density lipoprotein-cholesterol (TG/HDL-C) ratio and Triglyceride-Glucose (TyG) indices, are important to normal and diabetic subjects.

### *1.1 Aim and Objectives of the Study*

**Aim:** The aim of this study is to propose a new system of comparative study of diabetes mellitus indices of normal, pre-diabetic and diabetic human patient in predicting and monitoring or controlling diabetes mellitus.

**Objectives:** Theobjectives of the study include to:

1. Use Bio-data to investigate the association between Insulin resistance and diabetes, and to compare the effect of these pathological conditions on human subjects.
2. Investigation of Insulin, HbA1c, Glucose, TSH, fT3, fT4 on the normal, pre-diabetic and diabetic human subjects.
3. Haematological indices: FBC or complete blood count (CBC) which comprises all the haematological indices.

### *1.2 Significance of the Study*

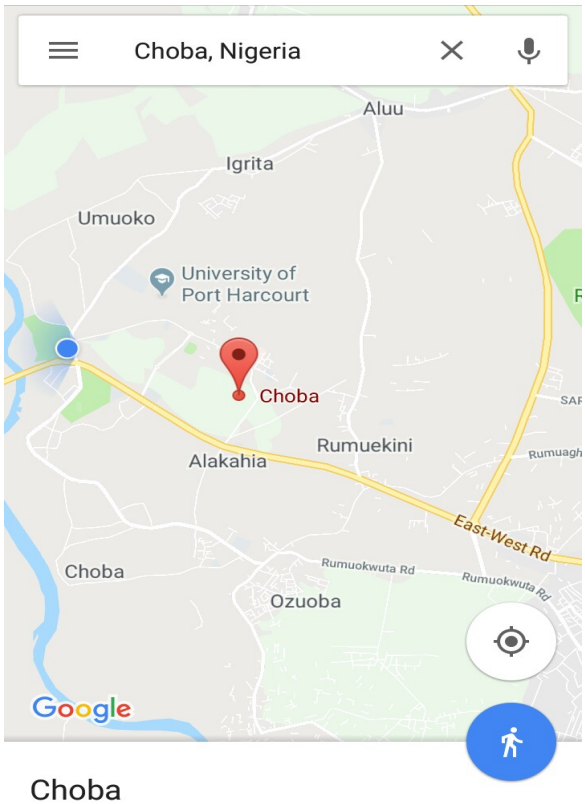
Base-line data could be provided for physicians in the assessment of insulin resistance, and management of diabetes.

This study intends to make available some scientific information on Glucose, insulin, HbA1c, FBC, TG/HDL cholesterol index or ratio, TSH, fT3, fT4, TyG index, HOMA-IR index, of normal and diabetic subjects. Subjects with high TyG index have a high risk of diabetes. Insulin resistance (IR) is associated with an increased risk of hyperglycemia, hypertension, and dyslipidemia, which increases the risk of inflammation, altered coagulation, and atherosclerosis.

Many studies have demonstrated that IR is one of the most important contributing factors to CVD (Hanley *et al*., 2002; Bonora*et al*., 2007).Furthermore, given that insulin resistance is an important risk factor for development of type 2 diabetes and incident cardiovascular diseases, identification of subjects with insulin resistance is a strategy for identifying high-risk people for targeted preventive interventions (Hanley *et al*., 2002; Rutter*et al*., 2005).

## II. STUDY AREA

The study area includes: Choba, University of Port Harcourt (Uniport) campuses, and University of Port Harcourt Teaching Hospital (UPTH), all in Obio/Akpor Local Government Area of Rivers State, Nigeria. It also includes Aluu in Ikwerre Local Government Area of Rivers State, Nigeria. The study area is located in the Niger Delta region, bordering the Atlantic Ocean. The area lies approximately in latitudes 6°54′N and longitudes 4°53′E (Plate 1.1).




Choba

Plate 1.1 Map of the Study Area (Google)

## III. MATERIALS AND METHODS

### *3.1 Experimental Human Design*

The following approach was employed in grouping the human subjects; the subjects were majorly grouped into two: control GROUP A, and test Groups B and C. Group A is the control group consisting of forty (40) normal (non-diabetic) subjects.Group B is the test group consisting of 40 pre-diabetic subjects while Group C is another test group consisting of 40 diabetic subjects.

*Inclusion criteria for human subjects:*

**a.** Subjects aged between thirty six (36) to seventy six (76) years who agreed to participate in the research.

*Exclusion criteria for human subjects:*

**a.** Subjects with co-infection with other metabolic disorders.

### *3.2 Population of the Study*

*Study population selection for human subjects:*

It consisted of normal and diabetic subjects mainly in the University of Port Harcourt teaching hospital (UPTH).

The entire population size was one hundred and twenty (120) individuals.

*Sample size determination for human subjects:*

The minimum sample size was calculated employing the formula below (Anderson *et al.*, 1991):

$N = Z^2 (pq) / e^2$

Where N = minimum sample size,

Z = 1.96 at 95% confidence limits, so that $z^2 = 3.8416$

p = prevalence of increased normal and diabetic subjects' percentage average

q = 1-p

### *3.3 Blood Sample Collection and Preparation*

*Preparation before commencement of analysis*

1. Subjects were issued or given the informed consent form to fill after listening to a detailed explanation from the researcher.

2. Five (5) ml of blood samples was collected using 5 ml syringe from each subject. Two (2) ml was put into Lithium heparin Bottle, 2 ml into plain bottle and 1ml into Fluoride oxalate bottle.

3. The sample was placed in sample racks and left to stand for at least thirty (30) minutes at room temperature.

4. The sample was centrifuged for 5 minutes using the centrifuge, Hettich Universal 320 at room temperature and a completely cell free non-haemolysed sample was obtained.

5. The samples were then seperated into a one (1) ml sample container which were labelled with the serial number of the subject, and left to refrigerate before use.

*Information sources and search strategy*

Published studies that assess insulin resistance between normal and diabetic subjects (especially T2DM) were searched in MEDLINE, EMBASE and PubMed databases covering the period from 2000 to 2018. Literature search was then carried out using the combination of terms “insulin”, “insulin resistance”, “TG/HDL ratio”, “HOMA-IR”, “HbA1c”, “TyG”, “Blood sugar”, "diabetes", "diabetes mellitus", "type II diabetes", "T2D", "T2DM", "type 2 DM", "IGT", "risk factor", "epidemiology", "review". The reference lists of the retrieved articles and reviews of this field (Shepard *et al.*, 2005; Negro, 2006; White *et al.*, 2008; Negro &Alaei, 2009) were also searched. The search was limited to human studies and English publications.

*3.4 Analysis*

*Biochemical Analysis*

The Bio-data comprising the Blood pressure (Systolic and Diastolic) and BMI was analysed. Also, Blood Glucose were analysed using Randox Kits (RANDOX, USA). HbA1c test was analysed using WondfoFinecare System (WONDFO, CHINA). Insulin was analysed using Calbiotech Inc., enzyme-linked immunosorbent assay (ELISA) Kit while Thyroid Function was analysed using Accubind Elisa Kits (ACCUBIND, USA). The homeostatic model and other indices were also analysed.

*Haematological Analysis*

Full blood count (FBC) comprising the Red Blood Cell (RBC) count and its components alongside Platelet levels, and the White Blood Cell (WBC) count and its components were analysed.

*Determination of Blood Pressure (BP)*

Blood pressure (BP) was measured on the right arm in the sitting position using a standard mercury sphygmomanometer after at least 5 minutes of rest. The first and fifth Korotkoff sounds were recorded (Pan *et al*., 1997).

*Determination of Body Mass Index (BMI)*

Body weight, height and circumference of waist and hip were measured with standard methods (Pan *et al*., 1997). Body weight was measured with electronic scales to the nearest 0.1 kg. Body height was measured to the nearest 0.1 cm by using a stadiometer (Pan *et al*., 1997). BMI was calculated as weight in kilograms divided by height in meters squared ($kg/m^2$).

*3.5 Statistical analysis*

All data were subjected to statistical analyses. Statistical analysis was performed using SPSS version 21 (IBM, U.S.A). The data was analyzed using one-way analysis of variance (ANOVA) and significant differences were determined using post Hoc Duncan multiple comparison test ($p<0.05$). The results were considered significant at 95% confidence level. The values were represented as mean ± standard error mean (SEM).

## IV. RESULTS

*4.1.1 - Bio data of human subjects*

The results obtained for the bio-data was presented.

120 subjects made up of 40 non-diabetics, pre-diabetics, and diabetics (3 groups of subjects) respectively were recruited for the study. The sub groups comprised 20 non-diabetic males and females respectively, 19 pre-diabetic males and 21 pre-diabetic females, and 20 diabetic males and females respectively. The height, weight, and other bio-information such as the age were used to determine the BMI of the individual subjects involved in the study. The same table showed the blood pressure of the 3 groups of subjects. The height of the non-diabetic and diabetic groups was not significantly different (176.20±1.25cmand 173.47±0.93cm), but the height of the pre-diabetics (170.82±1.09cm) was significantly different ($p \leq 0.05$) 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 different ($p \leq 0.05$) from 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 ($p \leq 0.05$) 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) differed significantly ($p \leq 0.05$) from that of the non-diabetics (110/72 mmHg). Systolic pressure of the diabetics was also statistically different ($p \leq 0.05$) from that of the pre-diabetics but the diastolic pressure was not statistically different ($p > 0.05$), 119/75 mmHg and 112/74 mmHg respectively.

The results obtained for the bio-data are presented in Figure 4.1 below.

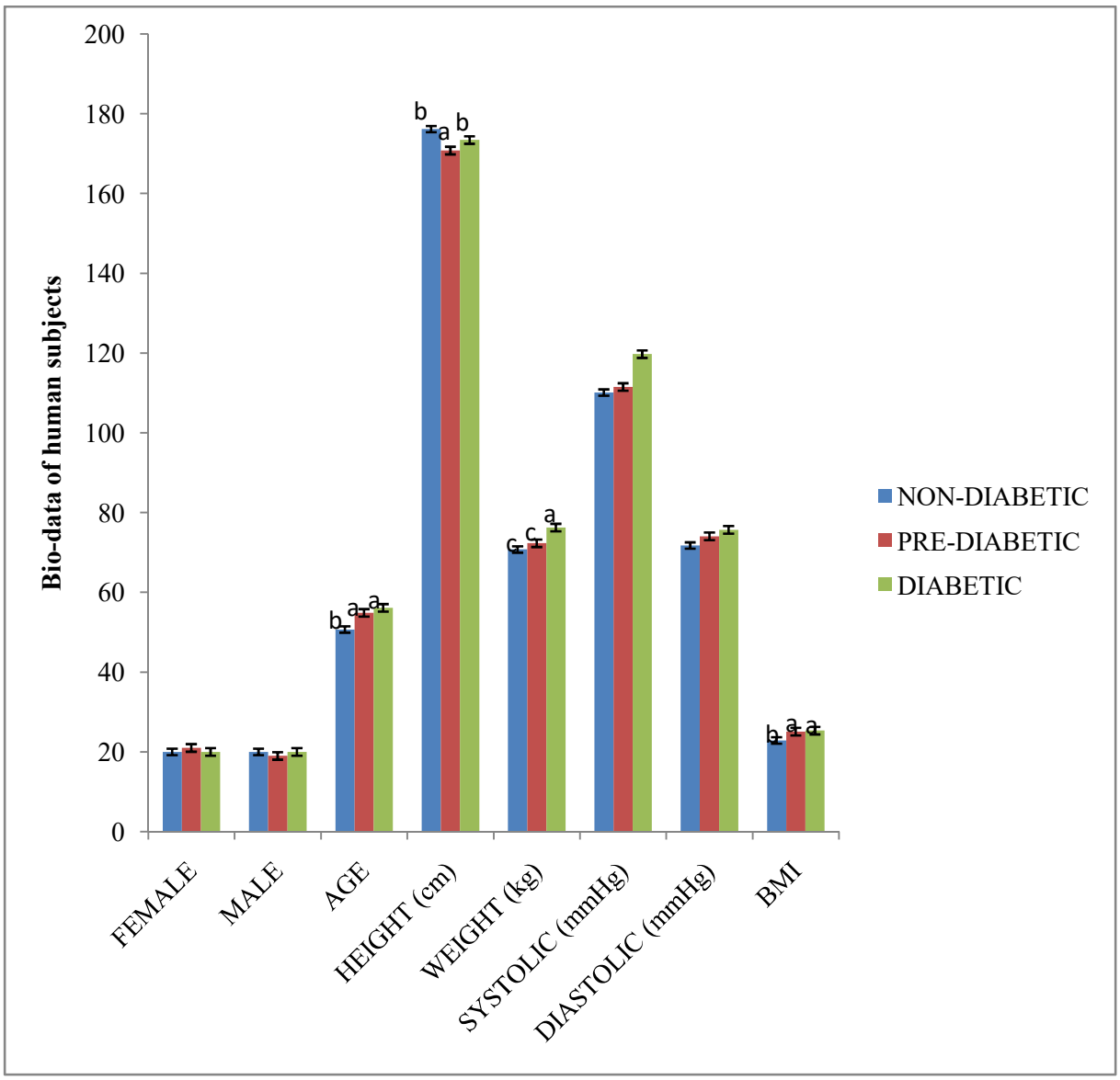



**Figure 4.1** Bio-data of human subjects for the non-diabetic control, pre-diabetic, and diabetic groups.

Data are expressed as Mean ± Standard error mean (SEM), n=120 where n represents the number of human subjects. Values found in a column with common superscript letter a, are significantly different ($p \leq 0.05$) when compared to the non-diabetic. Values with the superscript b, are significantly different ($p \leq 0.05$) relative to the pre-diabetic. Values with the superscript c, are significantly different ($p \leq 0.05$) compared to the diabetic group.

Where:

F – Female; M – Male; BMI – Body Mass Index

*4.1.2 - Some Glycemic indices and Hormonal profiles of the Human subjects*

Glucose (GLU) and HbA1c (Glycemic indices), Insulin (INS) and Thyroid Function profile ((free triiodothyronine (fT3) and free thyroxine (fT4)) of the human subjects are shown in Figure 4.2.

The Glucose and HbA1c showed a 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 statistically different ($p \leq 0.05$) across the groups for both Glucose and HbA1c. Insulin levels were also statistically different ($p \leq 0.05$) 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. The fT3 and fT4 showed progressive decrease in values having values of 3.22±0.11

pmol/L, 3.0±0.12 pmol/L, and 2.61±0.09 pmol/L for fT3; and 1.11±0.05 ng/dL, 1.07±0.06 ng/dL, and 0.97±0.05 ng/dL for fT4; respectively for the non-diabetics, pre-diabetics, and the diabetics while the TSH values increased significantly when compared to the normal. TSH for the pre-diabetic group was however slightly higher than that for the diabetics as shown in Figure 4.2 below.

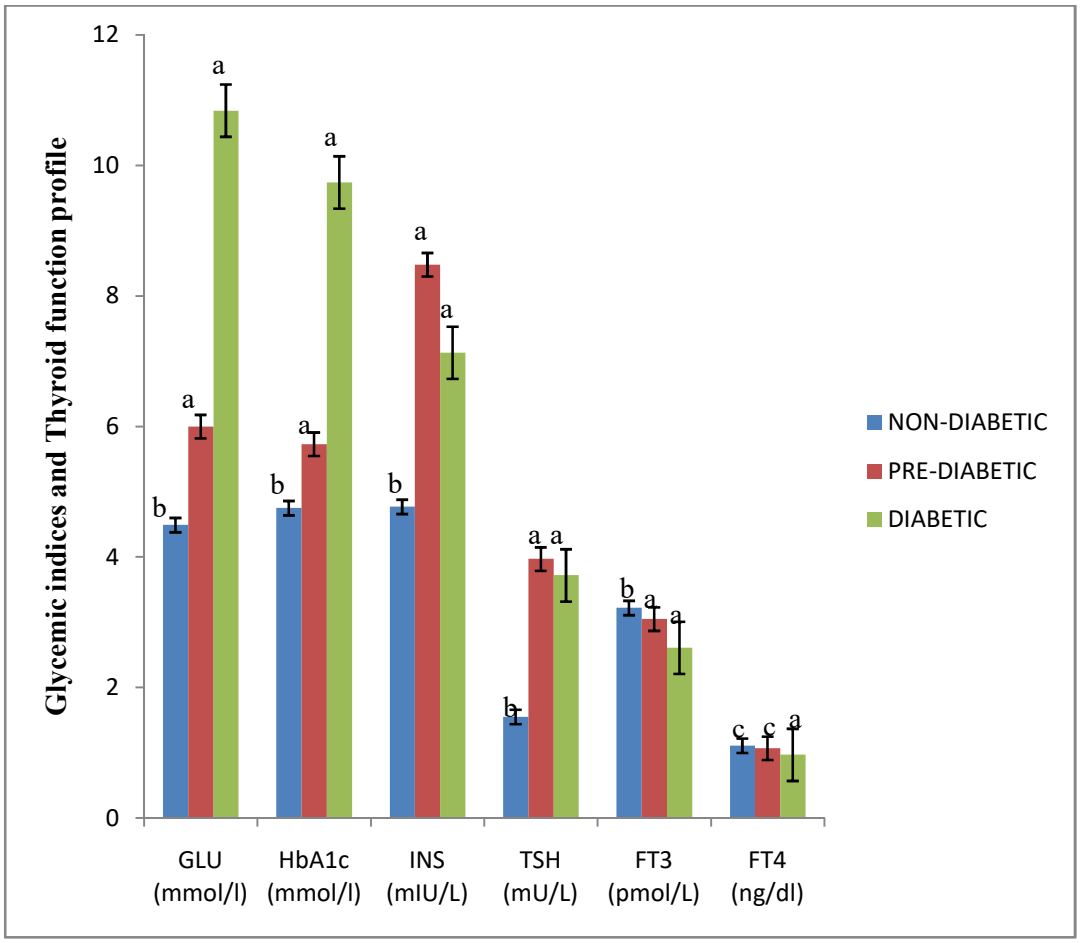



**Figure 4.2**Glucose and HbA1c (Glycemic indexes), Insulin and Thyroid Function profile of the human subjects

Data are expressed as Mean ± Standard error mean (SEM), n=120 where n represents the number of human subjects. Values found in a column with common superscript letter a, are significantly different (p≤0.05) when compared to the non-diabetic. Values with the superscript b, are significantly different (p≤0.05) relative to the pre-diabetic. Values with the superscript c, are significantly different (p≤0.05) compared to the diabetic group.

Where:

GLU – Glucose; HbA1c – GlycatedHaemoglobin; INS – Insulin; TSH – Thyroid Stimulating Hormone; fT3 – Free Triiodothyronine; fT4 – Free Thyroxine

*4.1.3 - Haematological Profile of the Human Subjects*

Figure 4.3 below is the Haematology result of the human subjects. Table 4.6 below shows the Red Blood Cell (RBC) count and its components alongside platelet count of the human subjects used in this study. RBC was significantly higher (p≤0.05) in the diabetic subjects. The values were 4.29±0.07 mL, 4.38±1.05 mL, and 4.90±0.11 mL for the non-diabetic, pre-diabetic and diabetics respectively. Hb and PCV were not statistically different (p>0.05) across the groups though the non-diabetic patients had a slightly lower Hb and PCV than the other groups. Platelet (PLT) count, on the other hand, were 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.

The White Blood Cell (WBC) count and its components (Neutrophils, Lymphocytes, Monocytes, Eosinophil and Basophils) in the human subjects were shown. 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 the non-diabetics and pre-diabetics with

values of 25.20±0.59 cells/µL, 26.37±1.48 cells/µL, and 9.47±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 ($p \leq 0.05$) in the diabetic group. Eosinophil count increased progressively across the groups with the increase being significant ($p \leq 0.05$) 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 figure 4.3 below.

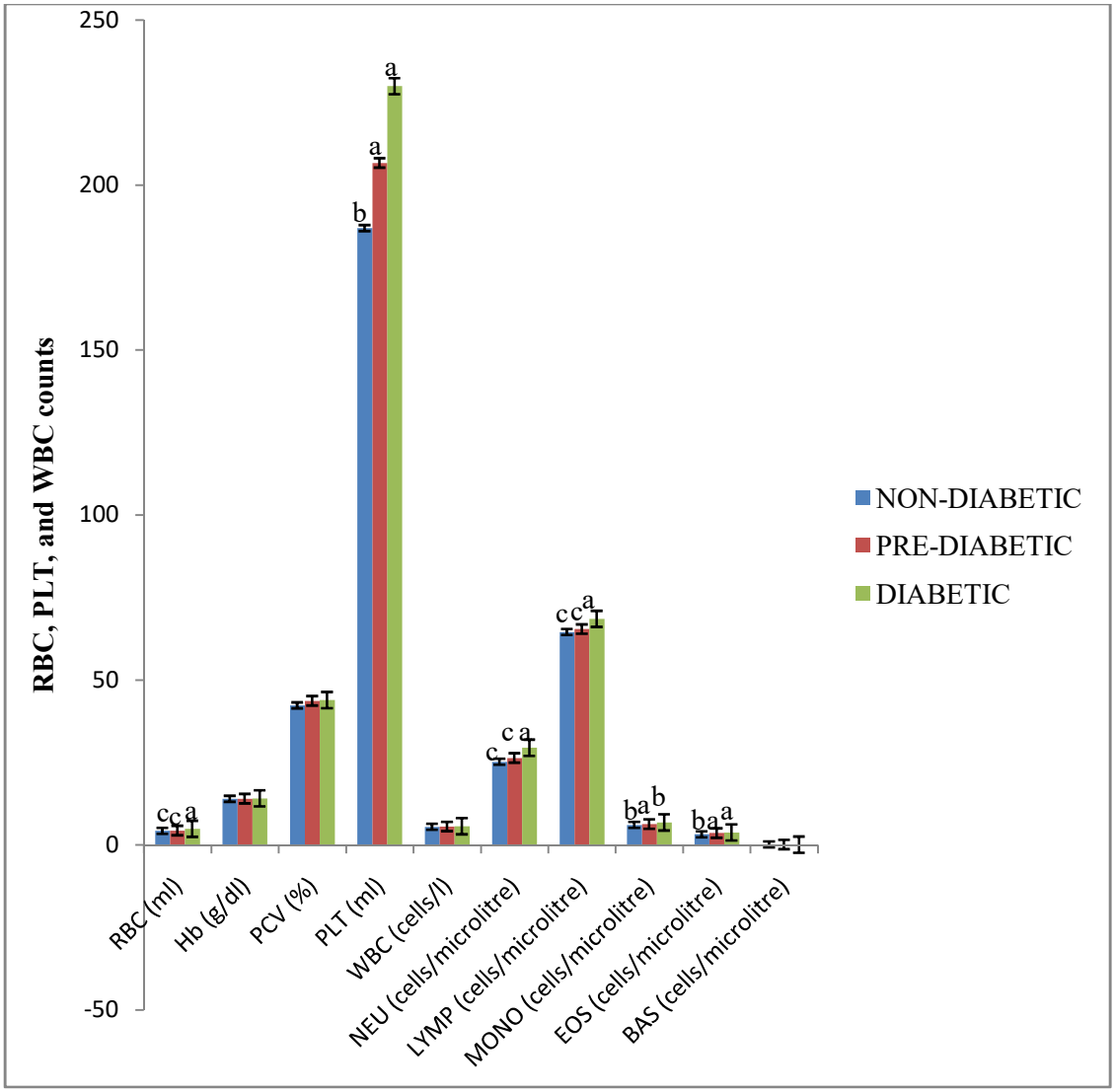



**Figure 4.3** RBC, WBC counts and their components alongside PLT count in Human subjects

Data are expressed as Mean ± Standard error mean (SEM), n=120 where n represents the number of human subjects. Values found in a column with common superscript letter a, are significantly different ($p \leq 0.05$) when compared to the non-diabetic. Values with the superscript b, are significantly different ($p \leq 0.05$) relative to the pre-diabetic. Values with the superscript c, are significantly different ($p \leq 0.05$) compared to the diabetic group.

Where:

RBC – Red Blood Cell, Hb – Haemoglobin;PCV – Packed Cell Volume, PLT – Platelet

WBC – White Blood Cell, NEU – Neutrophil; LYMP – Lymphocyte, MONO – Monocyte

EOS – Eosinophil, BAS – Basophil

*4.2 Discussion*

This research tends to study human model to intensively assessthe insulin resistance in normal and diabetic subjects using homeostatic model and other indices. There is a correlation between diabetes and the 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 up to 80 times more likely to develop type 2 diabetes than those with a BMI of <22 (McGill, 2005). Insulin sensitivity is a continuous variable. Thus young, lean, physically fit individuals are likely to be highly insulin sensitive whereas obese subjects with type 2 diabetes will have poor insulin sensitivity (Greeve, 2005).This is supported by the bio-data obtained from the subjects used in this research. 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 BP as the BP increased significantly across the normal, pre-diabetic and diabetic subjects in a similar order. Other risk factors such as genetics, ethnicity and age are also correlated to type 2 diabetes but were not considered in this work. Type 2 diabetes has a direct correlation with an increased risk of visceral fat deposition (Simmons, 2019). 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 has been shown to improve blood glucose levels (McGill, 2005), and has allowed people with type 2 diabetes to come off or avoid going onto insulin resistance. Obesity is also thought to trigger 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 metabolic condition that usually results in type 2 diabetes (Bray, 2004).

In this study, we found that insulin resistance was increased significantly in the pre-diabetic and diabetic groups as depicted by the HOMA-IR index in the human subjects. This is expected and in line with other studies as it is known that insulin resistance is a major risk factor and predicts Type 2 diabetes (Bray, 2004).

Analysis of thyroid function (TSH, fT3 and fT4) in the human subjects showed that the thyroid function of pre-diabetics and diabetics differed significantly from that of the normal non-diabetic subjects. There was a significant increase in the TSH of the pre-diabetic and diabetic subjects and this increase was highest in the pre-diabetic subjects which suggests that the diabetic subjects may have already taken intervention measures. The complications of diabetes reduce mostly as intervention measures are taken and prevention of long term complications is the one of the major reasons of drug and lifestyle interventions in diabetes patients (Greenapple, 2011). On the other hand, fT3 and fT4 were decreased in the pre-diabetic and diabetic state. The decrease in fT3 and fT4 followed the glycaemic state as indicated by the Glucose and HbA1c levels and was lowest in the diabetic subjects. Thyroid dysfunction is widely reported in diabetes (Ogbonna&Ezeani, 2019). Diabetes mellitus and thyroid dysfunctions are two commonly encountered endocrine disorders encountered in the hospital clinic. Both insulin and thyroid hormones are antagonistic in their actions. In a hospital-based study in India, 20% of diabetic patients were found to have hypothyroidism. Insulin resistance was significantly higher in the hypothyroid patients and TSH was positively correlated with insulin resistance (Chutia*et al*., 2018, Ogbonna&Ezeani, 2019). Our study was in agreement with this as we found TSH to be higher in the pre-diabetic and diabetic groups with increased Glycaemia as represented by the Glucose and HbA1c concentrations. TSH also increased significantly with increased insulin resistance as measured by their HOMA-IR and the TYG and TG-HDL indexes.

Analysis of the haematological parameters in the human subjects in this study showed that there were alterations in the haematological indices in the diabetic state. Diabetes is a metabolic disease that is characterized by hyperglycaemia, dyslipidemia, hypertension, and impaired hematological indices. Several hematological changes affecting the red blood cells (RBCs), white blood cells (WBCs), and the coagulation factors are shown 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. It was stated that this might be partly explained by the increased HbA1c in the diabetic state (Marar, 2011). In this study, HbA1c of the diabetic patients were also higher than that of the controls. Platelet count and WBC count and its components were also found to be elevated in the pre-diabetic and diabetic subjects relative to the normal control group. This is in agreement with findings reported by several previous 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 might also be the result of the increased oxidative stress triggered by the high levels of hyperglycemia in the diabetic patients. In contrast to this study, some other study have actually reported a 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. Diabetics with long term complications such as Diabetic Nephropathy will also have reduced kidney function and

reduced production of erythropoietin and ultimately decreased RBC count. In this study, age of diabetics were not considered.

## V. CONCLUSION

Based on our findings, the assessment of insulin resistance studied using the human subject model proved that insulin resistance can be managed when appropriate lifestyle is adopted. Recognition and monitoring of insulin resistance in the normal and diabetic patient will likely lead to a more successful preventive approach and a better therapeutic intervention measure and management of the diabetic patient.The human model was designed and used to assay various biochemical and haematological parameters and the findings largely corroborated previous studies with few exceptions.

## VI. RECOMMENDATIONS

It is recommended that this research should be further carried out using larger human samples size. The research also should be carried out, not only on one ethnic group or location as variation in geographical location affects the genetic factor and limit the generalization of the research findings.

## CONTRIBUTIONS TO KNOWLEDGE

This research studied various human subjects in the assessment of insulin resistance. It also went out of the normal to look at other parameters such as TSH, fT3 and fT4. This research compared the blood analytes of non-diabetics, pre-diabetics and diabetics to monitor the onset of diabetes and proffer possible solutions to enhance early detection and treatment of the type 2 form of diabetes.

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