ISSN: 2476-8642 (Print)
ISSN: 2536-6149 (Online)
www.annalsofhealthresearch.com
African Index Medicus, Crossref, African Journals Online, Scopus, C.O.P.E & Directory of Open Access Journals

Annals of HEALTH RESEARCH

(The Journal of the Medical and Dental Consultants' Association of Nigeria, OOUTH, Sagamu, Nigeria)

Volume 11 | No. 2 | Apr. - Jun., 2025

IN THIS ISSUE

PUBLISHED BY THE MEDICAL AND DENTAL CONSULTANTS ASSOCIATION OF NIGERIA, OOUTH, SAGAMU, NIGERIA.
www.mdcan.oouth.org.ng

Annals of Health Research

(The Journal of the Medical and Dental Consultants Association of Nigeria, OOUTH, Sagamu, Nigeria)

Volume 11, Issue 2: 174-183
June 2025
doi:10.30442/ahr.1102-07-283

ORIGINAL RESEARCH

Evaluation of Some Thrombogenic Parameters Among Type 2 Diabetes Mellitus Patients in Sagamu, Nigeria

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Citation: Amballi AA, Olooto EW, Osho AO, Oyewole OG, Onayemi AA, Olawore IP. Evaluation of Some Thrombogenic Parameters Among Type 2 Diabetes Mellitus Patients in Sagamu, Nigeria. Ann Health Res 2025;11:174-183. https://doi.org/10.30442/ahr.1102-07-283.

Abstract

Background: Metabolic dysfunction in type 2 diabetes mellitus (T2DM) is related to defective glucose metabolism, deficient synthesis of fatty acids and triglycerides, and compensatory switch to the use of protein and fat in search of alternative metabolic fuel. Complications arising from this metabolic disorder include angiopathy, among others.
Objective: To examine the pattern of some thrombogenic parameters in Type 2 Diabetes mellitus.
Method: A comparative, cross-sectional study of non-obese, obese Type 2 diabetic patients as the test population and a subset of healthy, non-diabetic individuals as controls. Anthropometric parameters were measured, and body mass index (BMI), waist-to-hip ratio (WHR), and percentage body fat (%BF) were computed for tests and controls. Fasting serum triglycerides, total cholesterol, high-density lipoprotein (HDL), high sensitivity C-reactive protein (hs-CRP), and interleukine-6 (IL-6) were measured, and low-density lipoprotein (LDL) was calculated for all participants.
Result: A total of 150 participants, with an age range of 41-60 years. Significantly higher values of ($p<0.001$) weight, BMI, WC, HC, %BF, WHR, serum glucose, HbA_{1c}, leptin, triglycerides, cholesterol, LDL, hs-CRP and IL-6 levels were observed. A significantly lesser value of serum A1AT, adiponectin, and HDL levels amongst the people with diabetes when compared to the control subjects ($p<0.001$), more in obese individuals with diabetes ($p<0.001$).
Conclusion: It is evident from this study that T2DM is associated with dyslipidaemia and increased serum levels of inflammatory and thrombosis markers, suggesting that risk factors of thrombotic events exist in Type 2 Diabetes mellitus patients.

Keywords: α1-Antitrypsin, Adiponectin, Inflammatory markers, Thrombosis, Type 2 Diabetes mellitus.

Introduction

Fasting and postprandial normoglycaemic state is a function of the balance between insulin activities and that of counter-regulatory hormones. Insulin resistance activities at hepatic and skeletal muscle levels and insulin deficiency from β-cell dysfunction result in Type 2 Diabetes mellitus (T2DM), characterized by chronic hyperglycaemia. Between the T2DM and normoglycaemic states is an impaired glucose tolerance (IGT) state, which may progress to T2DM with contributions from genetic, host-related, and environmental factors. T2DM constitutes 90-95% of cases among the different clinical types. [1]

The primary metabolic dysfunction in T2DM is related to the pathognomonic defective glucose metabolism, deficient synthesis of fatty acids and triglycerides, and compensatory switch to using protein and fat in search of alternative metabolic fuel. Defective cellular glucose uptake secondary to insulin deficiency or resistance results in suppressing enzymes in the glycolytic, lipogenic, and pentose phosphate pathways and stimulation of gluconeogenic, glycogenolytic, and lipolytic pathways. [2] Consequently, there are reduced metabolic activities in the hepatocytes and skeletal muscle and compensatory increased activities in the adipose tissue, releasing metabolically active adiponectin with hormonal, anti-inflammatory, β-cell function stimulation and insulin-sensitizing properties. [3] Changes in adipose tissue functions in conditions such as obesity, characterized by visceral adipose tissue accumulation, increase the risk of developing T2DM. [4, 5]

The discovery of high levels of inflammatory markers in clinically overt T2DM suggests the involvement of inflammation in the pathogenesis of the disease and the development of hyperglycaemia-induced complications. The need to study the risk factors of angiopathy in T2DM cannot be over-emphasized. Venous thromboembolism (VTE) is the most prevalent acute cardiovascular illness after a heart attack or stroke. VTE is four times more prevalent in high-income nations than in low-income countries. [6 - 8] While hypoadiponectinaemia correlates with insulin resistance and T2DM development, hyperadiponectinaemia is associated with a low risk of developing T2DM. [9]

The abnormal metabolism of fats resulting in hypertriglyceridaemia and increased serum free fatty acid levels occurring in diabetes predisposes people with diabetes to increased thrombotic events. Several major observational studies have identified high body mass index (BMI) as a risk factor for VTE. [10 - 12] A recent study reported that the circulating leptin level was a risk factor for VTE, DVT (Deep Vein Thrombosis) and PE (Pulmonary Embolism) and that adiponectin was a potential protective factor for both VTE and PE. [13] Substances potentially involved in thrombosis include leptin, adiponectin, resistin, plasminogen activator inhibitor-1, tissue factor angiotensin II, non-esterified free fatty acids, LDL, TNF-α, CRP, A1AT, transforming growth factor-b, and IL-6. [14] Elevated serum leptin, PAI-1, tissue factor, TNF-α, IL-6, and MCP-1 and decreased A1AT and adiponectin had been reported to increase inflammatory processes, thrombotic tendencies and may exacerbate the risk of developing atherothrombosis. [15] People with T2DM are thus prone to developing thrombotic crises, complicating the existing chronic hyperglycaemic state. This study, therefore, investigated the pattern of some of these thrombogenic parameters in Type 2 DM patients to assess any likely existing risk factors of thrombotic events in the condition.

Methods

Study design

The study design was comparative, cross-sectional and case-control.

Study setting

The study was conducted at the General Outpatient Department (GOPD) of the Olabisi Onabanjo University Teaching Hospital (OOUTH) Sagamu. The data were collected from 8th January to 27th February, 2024.

Ethical consideration

Ethical approval for the study was obtained from the Health Research Ethical Committee of Olabisi Onabanjo University Teaching Hospital Sagamu (OOUTH/HREC/734/2023AP). Written informed consent was obtained from all participants before the commencement of the study.

Study population

Newly diagnosed Type 2 DM cases (obese and non-obese) patients were recruited as the test group, and normoglycemic subjects were recruited as controls. One hundred and fifty participants (age range of 41-60 years) comprising 50 non-obese T2DM and 50 obese T2DM were recruited as the test group, while 50 healthy non-diabetic individuals were recruited as controls. The participants were randomly selected among adults attending the General Outpatient Clinic. The test group was newly diagnosed T2DM patients (male and female). In contrast, the control group was chosen among individuals who accompanied the patients to the clinics and some hospital workers. Obesity was defined as BMI >30 kg/m^2, and diabetes was defined as FBG > 126 mg/dL (7 mmol/L).

Inclusion and exclusion criteria

Included in the study were consented newly diagnosed T2DM patients and healthy control subjects, with an age range of 41-60 years. Excluded from the survey were T2DM patients or control subjects with acute infections, chronic ailments such as malignancy, renal failure, liver cirrhosis, connective tissue disease, and chronic congestive heart failure, and diagnosed T2DM patients who had commenced drugs.

Biophysical parameters

Body weight, height, hip circumference (HC), and waist circumference (WC) were measured using universally accepted methods and taking necessary precautionary measures. Body mass index (BMI), waist-to-hip ratio (WHR), and percentage body fat (%BF) were computed for the test and control groups. The calculations were as follows: BMI = Weight /Height^2; WHR = WC/HC; and %BF = [(1.2 x BMI) + (0.23 x age) – 16.2].

Tissue sample collection and storage

Ten millilitres (10 mL) of fasting venous blood (8-10 hours overnight fast) were drawn from all participants using the antecubital vein with a pyrogen-free needle and syringes. The blood samples were drawn into plain bottles, allowed to clot, and centrifuged at 5000 rpm for five minutes to obtain the serum, which was separated into sterile plain bottles. Two millilitres (2 mL) of serum were used to determine high sensitivity C-Reactive Protein (hs-CRP) immediately after separation while the remaining sample was stored at -20°C until assayed.

Biochemical analysis

Fasting serum triglycerides, total cholesterol, high-density lipoprotein (HDL), hs-CRP, and interleukine-6 (IL-6) were measured using respective ELISA kits supplied by Abcam, based on standard principles and methods. [16-20] Serum glucose, glycated haemoglobin, α1-antitrypsin (A1AT), adiponectin, and leptin were determined using standard methods. [21-25] The low-density lipoprotein (LDL) was calculated. [16]

Statistical analysis

The data were analyzed using the Statistical Package for Social Sciences (SPSS) software version 25. Descriptive statistics and bar charts were used to represent information. Differences in mean between the groups were compared using one-way ANOVA, and differences in values were considered statistically significant at $p < 0.05$.

Results

Table I shows that the body mass index and waist-to-hip ratio were significantly higher in patients with Diabetes mellitus compared with the control group, and the difference was more pronounced in the obese T2DM group than in the non-obese T2DM group.

Table I: Anthropometric indices of participants

Parameters	*Control*	*Test*		*F*	*p-value*
		Non-Obese	**Obese**		
Age (years)	55.18±1.40	59.92±1.18	57.88± 0.95	3.987	0.021
Weight (kg)	67.06±2.53	78.22±1.01	89.16±0.90	54.472	<0.001
Height (m)	1.64±0.01	1.64±0.01	1.65±0.01	0.718	0.489
BMI (kg/m2)	24.80±0.90	29.08±0.36	32.58±0.37	54.382	<0.001
WC (cm)	83.30±1.60	86.3±1.14	105.20±1.63	54.379	<0.001
HC (cm)	101.22±1.85	101.31±1.75	113.96±2.12	17.161	<0.001
WHR	0.82±0.01	0.85±0.03	0.92±0.02	78.189	<0.001
%BF (%)	26.26±1.11	32.48±0.55	36.21±0.45	58.036	<0.001

BMI - Body Mass Index, WC - Waist Circumference, HC - Hip Circumference, WHR - Waist-to-hip Ratio, %BF - Percentage body fat.

Table II suggests significantly higher fasting blood sugar, Haemoglobin A_1C and leptin in participants with T2DM compared with the control group. These significantly higher values were more prominent in the obese T2DM group than the non-obese T2DM group. On the other hand, alfa-1 anti-trypsin and adiponectin levels were significantly lower in the T2DM group compared with the control. These significantly lower values were more pronounced in the obese T2DM group than the non–obese T2DM.

Table III shows a significantly higher serum triglyceride level, total cholesterol and low-density lipoprotein in the T2DM group compared with the control group. There were significantly lower serum levels of high-density lipoprotein in the T2DM group compared with the control group. The lowered levels were significantly more pronounced in the obese T2DM group than in the non-obese group.

There were also significantly higher serum levels of inflammatory markers, the high sensitive C-reactive protein and interleukin - 6, in the T2DM group compared to the control group. These higher levels were more pronounced in the obese T2DM group than in the non-obese T2DM group.

Table II: Serum thrombotic indices among participants

Parameters	*Control*	*Test*		*F*	*p-value*
		Non-Obese	**Obese**		
FBG (mmol/L)	4.46±0.13	7.570.90	10.12±0.31	214.738	<0.001
HbA1c	2.28±0.11	5.93±0.11	8.39±0.14	690.624	<0.001
A1AT (mg/mL)	3.70±0.13	2.40±0.03	1.61±0.05	170.423	<0.001
Adiponectin (ng/mL)	10.04±0.11	8.19±0.09	5.27±0.09	604.926	<0.001
Leptin (ng/mL)	4.15±0.18	7.07±0.11	10.05±0.18	448.011	<0.001

FBG - Fasting Blood Glucose, HbA_{1c} - Glycated Haemoglobin, A1AT - α1-antitrypsin.

Table III: Serum lipid and inflammatory markers among participants

Parameters	*Control*	*Test*		*F*	*p-value*
		Non-Obese	**Obese**		
Triglycerides (mg/dL)	100.64±2.96	120.74±2.21	136.82±2.87	44.943	<0.001
Cholesterol (mg/dL)	143.69±5.40	184.28±4.35	246.50±3.88	127.352	<0.001
HDL (mg/dL)	47.50±1.14	39.39±0.54	39.82±0.82	27.664	<0.001
LDL (mg/dL)	76.06±5.30	120.74±4.61	180.32±3.97	117.837	<0.001
hs-CRP	1.46±0.09	3.82±0.14	6.32±0.20	257.179	<0.001
IL-6	1.01±0.03	2.62±0.07	3.79±0.06	581.037	<0.001

HDL - High-Density Lipoprotein, LDL - Low-Density Lipoprotein, hs-CRP - High sensitivity C-Reactive protein, IL-6 - Interleukine-6.

Discussion

Anthropometric parameters, notably weight, BMI, WC, HC, and WHR, are adiposity indices, as progressive increases in their values increase the risk of developing adiposity-induced metabolic disorders. Healthy adiposity is defined as BMI 18.5–24.9 kg/m^2, WC < 88 cm and < 102 cm, and WHR values < 0.80 and < 0.95, respectively, for women and men. [26] Lean (BMI < 18.5 kg/m^2), overweight (BMI 25.0-29.9 kg/m^2), or obese (BMI ≥ 30.0 kg/m^2) people with gluteo-femoral fat accumulation have decreased triglyceride, fasting blood glucose and insulin concentrations; increased HDL concentrations, insulin sensitivity; and thus, reduced risk of T2DM. The risk of metabolic disorder is moderate with WHR 0.81–0.85 and 0.96–1.0, but high with WHR > 0.86 and > 1.0, respectively, for women and men, the risk being lower in people with large HC. [27]

This study reveals a significant increase in weight, BMI, WC, HC, %BF, and WHR amongst participants with T2DM compared to the control subjects. However, variation exists in the measured anthropometric parameters in the test group, higher in obese T2DM cases than in the non-obese group. This confirms the presence of central obesity in the test group, which is predominantly associated with increased upper body fat (subcutaneous and visceral) and a high risk of developing T2DM. Excessive body fat accumulation induces metabolic abnormalities and diseases, including atherogenic dyslipidaemia, non-alcoholic fatty liver disease (NAFLD), β-cell dysfunction, insulin resistance, prediabetes, and T2DM.

Serum glucose reflects a homeostatic balance between various enzyme-catalyzed pathways involving carbohydrates, proteins and lipids as dictated by physiologic and metabolic requirements. Fasting blood sugar levels greater than 126 mg/dL (7 mmol/L) is described as a hyperglycaemic state consequent to absolute or relative insulin deficiency, some degrees of insulin resistance, hyperactivities of counter-regulatory hormones, drug activities, malnutrition state like obesity, or physiologic state like pregnancy. The findings from this study reveal a significantly higher serum glucose level in the T2DM groups compared to the control group, strengthening the diagnosis of diabetes mellitus. Among participants with T2DM, serum glucose was higher in the obese group than in the non-obese group in the present study. The observed hyperglycaemia among non-obese participants with T2DM

occurs due to relative insulin deficiency secondary to β-cell dysfunction and consequent decline of insulin secretory function. However, multiorgan insulin resistance may be responsible for the observed hyperglycaemia among the obese T2DM participants.

Glycated haemoglobin measures the average blood glucose level over the preceding 60 - 90 days. [28] From the present study, a significantly high HbA_{1c} value was observed among participants with T2DM and worse in the obese group. This indicates a poorly controlled hyperglycaemic state and confirms the fact that the participants were probably not receiving antihyperglycaemic therapy, as they were newly diagnosed.

Alpha-1 anti-trypsin is a potent acute stress reactant anti-elastase protein primarily produced in the liver. Its clinical importance lies in its role in emphysema, panniculitis, and Wegener's granulomatosis. Beyond its anti-protease capacity, A1AT has been suggested to activate phosphatases, inhibit caspase activity and nitric oxide production, reduce endoplasmic reticulum stress responses, minimize epithelial barrier damage, and regulate IL8-mediated neutrophil chemotaxis. [29] Its role in metabolism and metabolic disorders is inferenced following the alteration of its activities in established T2DM and the discovery of high levels of degraded A1AT in the urine of T2DM cases with diabetic nephropathy. [30] This study observed a significant reduction in serum A1AT levels among participants with T2DM and worse in the obese group. A similar decrease in A1AT levels had been reported in non-obese diabetic mice, gestational diabetes mellitus, and T1DM, where plasma anti-trypsin capability progressively decreased with the duration of diabetes mellitus. [31] The observed reduction in A1AT results from existing insulitis, inflammatory-induced reduction in the functional mass of the β-cells, pancreatic β-cells apoptosis and subsequent decreased insulin secretion capacity. [32] Also, the increased insulin resistance causes compensatory functional β-cell hypertrophic changes and induction of hyperinsulinemia. [33]

The adipose tissue is an active endocrine organ that secretes various hormones known as adipokines. Adipokines are secreted into the circulation and regulate insulin sensitivity and glucose and lipid metabolism. [34] The lower serum adiponectin levels in the present study, worse in obese- than non-obese subjects with T2DM, corroborates the reported association of low adiponectin with increased risk of T2DM. [35] The observed decreased adiponectin among obese individuals with T2DM is due to reduced adiponectin synthesis following infiltration of adipose tissue by inflammatory cells, stimulating the production of pro-inflammatory adipokines, such as C-reactive protein (CRP), tumour necrosis factor-alpha (TNF-α), monocyte chemoattractant protein-1 (MCP-1), lipocalin-2, resistin and interleukins (IL-1β), and IL-6). [36] However, sustained elevation of inflammatory cytokines enhances insulin resistance and reduces insulin sensitivity, thereby impairing glucose and lipid metabolism. [36]

Leptin is pivotal in energy homeostasis, glucose metabolism and body weight regulation. [37] Circulating leptin is directly related to the total body fat as reflected by WC, WHR and BMI. [38] There are controversial reports on the levels of leptin in T2DM. While some researchers reported low [39] and high leptin levels, [40] some reported no difference in leptin levels between individuals with T2DM and the control subjects. [38] The higher serum leptin in obese- than non-obese T2DM individuals in this study corroborates a previous report. [40]

Diabetic dyslipidemia has reduced HDL and increased triglycerides, cholesterol, VLDL, and LDL. The finding of higher levels of triglycerides, cholesterol and LDL and lower levels of HDL in T2DM patients compared to the control subjects corroborates reported dyslipidaemia in diabetes mellitus. [41] The observed changes in serum lipid demonstrated dyslipidaemic changes that form the basis of

cardiovascular disorders complicating T2DM. The observed changes in serum lipid occur due to existing peripheral insulin resistance with resultant reduction of glucose uptake by the skeletal muscle and adipose tissue as well as inhibition of lipolysis, insulin-mediated decrease in ApoB secretion and increased ApoB degradation in the hepatocyte, decreased adipose tissue lipoprotein lipase activities resulting in hypertriglyceridaemia. The observed reduced serum HDL level among individuals with T2DM reflects associated increased cholesteryl ester transfer protein levels, which mediates the transfer and exchange of cholesteryl ester and triglyceride from HDL to VLDL, VLDL remnants, IDL, and LDL. These interactions increase the catabolism of HDL and its hepatic clearance and contribute to reduced HDL levels.

The patterns of thrombogenic parameters in this study reflect the upregulation of leptin, hs-CRP, and IL-6 and a decrease in A1AT and adiponectin levels. These changes may impair the mobilization and recruitment of vascular progenitor cells from the bone marrow and increase inflammatory processes and thrombotic tendencies among obese and non-obese individuals with T2DM. This may further exacerbate the risk of developing atherothrombosis, complicating T2DM. Lipids influence haemostasis by modulating the expression of fibrinolytic, rheologic, and thrombotic factors and their functions; they increase the clotting activities of factor VII, plasminogen activator inhibitor-1 (PAI-1) and stimulate platelet activation, tissue factor expression, vitamin K-dependent clotting factors (factors II, VII, IX, X, proteins C and S) and fibrinogen. Lipids also inhibit tissue factor pathway inhibitors (TFPI), limiting the activation of the extrinsic clotting pathway. The observed reduction in HDL levels among individuals with diabetes reduces the capacity to inhibit platelet and erythrocyte aggregation, reduces blood viscosity, and suppresses tissue factor and PAI-1 activities, thus favouring atherothrombotic activities. The observed increased leptin, hs-CRP, IL-6, LDL, cholesterol and decreased HDL, A1AT and adiponectin levels among individuals with T2DM. This pattern suggests that individuals with T2DM may be prone to thrombotic complications. Since the observed changes in markers of thrombotic events are more pronounced in the obese group, it may imply a possible higher risk of thrombotic complications.

Conclusion

T2DM is associated with dyslipidaemia and increased serum levels of inflammatory and thrombosis markers, suggesting that individuals with T2DM are prone to developing thrombotic complications. Since the observed markers of thrombotic events are more pronounced in obese individuals with T2DM than in non-obese individuals, it implies a higher risk of thrombotic complications in the former.

Acknowledgement: The authors wish to express appreciation to the members of staff and the patients of the Outpatient Department of the Olabisi Onabanjo University Teaching Hospital, Sagamu, for their support during data collection.
Authors' Contributions: AAA conceived and designed the study. AAA, OEW and OOA analyzed and interpreted the data. OEW and OOA drafted the manuscript, and all the authors revised it for sound intellectual content and approved the final version.
Conflicts of Interest: None.
Funding: Self-funded.
Publication History: Submitted 31 January 2025; **Accepted** 15 June 2025.

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