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EVALUATION OF LIPOPROTEIN A AND LIPID TETRAD INDEX PATTERN IN DIABETIC PATIENTS ATTENDING METABOLIC CLINIC IN THE FEDERAL MEDICAL CENTRE, OWERRI, IMO STATE

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ABSTRACT

Lipoprotein A levels and Lipid Tetrad Index pattern were evaluated in diabetes mellitus patients attending metabolic clinic in the Federal Medical Centre, Owerri, Imo State. Two hundred (200) subjects (120 diabetics (tests) and 80 non diabetic, (controls) were recruited for the study, all in the age group of 20 to 60 years. Samples were analysed using appropriate analytical methods and the statistical analysis was performed on Statistical Package for Social Science (SPSS) Windows version 20.0. Test of significance was determined using the student's t-test and the statistical significance was set at $p<0.05$. The results were expressed as Mean ± SD. The study showed a statistically significant ($p<0.05$) increase in lipoprotein A (mmol/L), and lipid tetrad index thus: (0.27±0.03; and 1.79±0.82) in the tests compared to the controls (0.17±0.03; and 0.49±0.24) respectively. This present study therefore, concluded that lipoprotein A [Lp (a)] levels, and lipid tetrad index play key

roles, and serve as a predictive index in the development of coronary artery disease, in diabetes mellitus, and that gender (sex) and age (years) had no effect on the assayed parameters. The routine evaluation of lipoprotein A in the management of diabetes mellitus is therefore recommended.

KEYWORDS: Lipoprotein A, Lipid tetrad index and Diabetic patients.

INTRODUCTION

Before three decades ago, it would seem far-fetched to associate micronutrients and molecules with disorders like diabetes mellitus; however, continuous studies have shown that these substances are essential in the proper functioning of the body systems and in maintaining healthy homeostatic conditions. A number of such micro-molecules which have also become disease markers have been suspected to have significant involvement in a variety of diseases and some have been implicated in the exacerbation of such diseases leading to more complicated outcomes. Such is the case with Lipoprotein A (Lp (a), in Diabetes Mellitus.

Diabetes Mellitus is caused by an absolute or relative insulin deficiency. It has been defined by the World Health Organization (WHO), on the basis of laboratory findings, as a fasting venous plasma glucose concentration greater than or equal to 7.0mmol/L (on more than one occasion or once in the presence of diabetes symptoms) or a random venous plasma glucose concentration greater than or equal to 11.1mmol/L. Sometimes an oral glucose tolerance test (OGTT) may be required to establish the diagnosis in equivocal cases (Crook, 2006). According to Nwosu (2009), it is a chronic fasting hyperglycaemia of over 7.0mmol Diabetes is a chronic condition that arises when the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin produced. It is a metabolic disorder |, characterized by disturbance in carbohydrate, lipid, and protein metabolism (Nwosu, 2009), with oxidative stress and inflammatory reactions as common denominators of the disorder (Capuzzi and Freeman, 2001). Lipoprotein A (Lp (a)) is a lipoprotein sub-class. It consists of an LDL-like particle and the specific apolipoprotein (a) [apo(a)], which is covalently bound to the apo B of the LDL like particle. Lp(a) plasma concentrations are highly heritable and mainly controlled by the apolipoprotein (a) gene (LPA) located on chromosome 6q26-27. Genetic and epidemiological studies have identified Lp(a) as a risk factor for atherosclerotic disease such as stroke (Reddy and Yusuf, 2008). It was discovered in 1965 by Kare Berg (McKeigue *et al,* 2009); and the human gene encoding apolipoprotein (a) was cloned in 1987 (Anon, 2006). The mechanism and sites of Lp(a) catabolism are largely unknown. Uptake through the LDL receptor is not a major pathway of Lp(a) metabolism. The liver cells are

assumed to take part in its production (Goel *et al.*, 2003;Rajappa *et al*, 2006,). Nevertheless, the kidney has been identified as playing a role in its clearance from the plasma. The physiological function of Lp(a) is still relatively unknown, although a function within the coagulation system seems plausible, given the aspect of the high homology between apo(a) and olasminoeen (Anon, 2006). Infact, the LPA gene is derived from a duplication of the plasminogen gene. Other functions have been related to recruitment of inflammatory cells through interaction with Mac-1 integrm. angiogenesis and wound healing. However, individuals with little or no Lp(a) seem to be healthy. Thus plasma Lp(a) is certainly not vital, at least under normal environmental conditions.

The structure of Tp(a) is similar to plasminogen and tissue plasminogen activator (tPA) and it competes with plasminogen for its binding site, leading to reduced fibrinogen. Furthermore, because Lp(a) stimulates secretion of plasminogen Activator Inhibitor-1 (PAI-1), it leads to thrombogenesis. Lp(a) also transports cholesterol which controls and thus contributes to atherosclerosis (Anon, 2006). In addition, Lp(a) transports the more Atherogenic pro inflammatory oxidized phospholipids which attract inflammatory cells to vessel walls(Ramchandran, 2001; Gopinath *et al.*, 2004), and leads to smooth muscle cell proliferation (France *et al.*, 2003). Extensive studies confirming a strong correlation between elevated Lp(a) and heart disease have led to the consensus that Lp(a) should be an important, independent predictor of cardiovascular disease (CVD) (Reddy, 2008). Animal studies have shown that Lp(a) may directly contribute to atherosclerotic damage by increasing plaque size, inflammation, instability, and smooth muscle growth (Enans *et al.*,2006). However, the lack of clinical correlation data have resulted in Lp(a) being largely ignored by clinical guidelines for assessing CVD.

Key: CE: Cholesterol Ester; FC: Free Cholesterol; KIV:-Kringle IV domain; KV: Kringle V domain; PL: Phospholipid; TG: Triglyceride.

The mechanism and sites of Lp(a) catabolism are largely unknown. Uptake via the LDL receptor is not a major pathway of Lp(a) metabolism (Rader *et al.*,1995; Knight *et al.*, 1999). The kidney has been identified as playing a role in Lp(a) clearance from plasma (Alberts *et al.*, 2007).

Function of Lipoprotein A

The physiological function of Lp(a)/apo(a) is still unknown. A function within the coagulation system seems plausible, given the aspect of the high homology between apo(a) and

plasminogen. In fact, the LPA gene derives from a duplication of the plasminogen gene *(McLean et al.*, 1987).

Other functions have been related to recruitment of inflammatory cells through interaction with Mac-1 integrin, angiogenesis, and wound healing.

However, individuals without Lp(a) or with very low Lp(a) levels seem to be healthy. Thus plasma Lp(a) is certainly not vital, at least under normal environmental conditions. Since apo(a)/Lp(a) derived rather recently in mammalian evolution -only old world monkeys and humans have been shown to harbour Lp(a) -its function might not be vital but just evolutionarily advantageous under certain environmental conditions, e.g. in case of exposure to certain infectious diseases (McLean *et a.*,, 1987).

Another possibility, suggested by Linus Pauling, is that Lp(a) is a primate adaptation to L-gulonolactone oxidase (GULO) deficiency, found only in certain lines of mammals. GULO is required for converting glucose to ascorbic acid (vitamin C), which is needed to repair arteries; following the loss of GULO, those primates that adopted diets less abundant in vitamin C may have used Lp(a) as an ascorbic-acid surrogate to repair arterial walls (Sotiriou *et al*,.,2006).

Lipoprotein (A) **and Disease**

High Lp(a) in blood is a risk factor for coronary heart disease (CHD), cerebrovascular disease (CVD), artherosclerosis, thrombosis, and stroke (Christian, 2003). The association between Lp(a) levels and stroke is not as strong as that between Lp(a) and cardiovascular disease (1). Lp-a concentrations may be affected by disease states, (for example kidney failure), but are only slightly affected by diet, exercise, and other environmental factors.

Most commonly prescribed lipid-reducing drugs have little or no effect on Lp(a) concentration. Results using statin medications have been mixed in most trials, although a meta-analysis published in 2012 suggests that atorvastatin may be of benefit (Takagi and Umemoto, 2012). Niacin (nicotinic acid) and aspirin are two relatively safe, easily available and inexpensive drugs known to significantly reduce the levels of Lp(a) in some individuals with high Lp(a); they should be used under the supervision of a qualified physician (Takagi and Umemoto, 2012).

High Lp(a) predicts risk of early atherosclerosis independently of other cardiac risk factors, including LDL. In patients with advanced cardiovascular disease, Lp(a) indicates a coagulant risk of plaque thrombosis. Apo(a) contains domains that are very similar to plasminogen (PLG). Lp(a)

accumulates in the vessel wall and inhibits binding of PLG to the cell surface, reducing plasmin generation which increases clotting. This inhibition of PLG by Lp(a) also promotes proliferation of smooth muscle cells. These unique features of Lp(a) suggest Lp(a) causes generation of clots and atherosclerosis (Caplice *et al.*, 2001).

Vegetarians have higher levels of Lp-a than fish eaters in one homogeneous tribal population of Tanzania raising the possibility that pharmacologic amounts of *fish* oil supplements may be helpful to lower the levels of Lp-a (Marcovina *et al.*,1999).

Some studies have shown that regular consumption of moderate amounts of alcohol leads to significant decline in plasma levels of Lp-a while other studies have not (Sharped *al.*, 1998).

Diagnostic Testing

Numerous studies confirming a strong correlation between elevated Lp(a) and heart disease have led to the consensus that Lp(a) is an important, independent predictor of cardiovascular disease (Nordestgaard *et al.*, 2010). Animal studies have shown that Lp(a) may directly contribute to atherosclerotic damage by increasing plaque size, inflammation, instability, and smooth muscle cell growth. Genetic data also support the theory that Lp(a) causes cardiovascular disease (Sharpe *et al.*, 1998; Kamstrap *et al.*, 2011). The European Atherosclerosis Society currently recommends that patients with a moderate or high risk of cardiovascular disease have their lipoprotein (a) levels checked. Any patient with one of the following risk factors should be screened.

1. premature cardiovascular Disease
2. familial hypercholesterolaemia
3. family history of premature cardiovascular disease
4. family history of elevated lipoprotein (a)
5. recurrent cardiovascular disease despite statin treatment
6. 3% 10-year risk of fatal cardiovascular disease according to the European guidelines
7. 10% 10-year risk of fatal and/or non-fatal cardiovascular disease according to the US guidelines (Nordestgaard *et al., 2010).*

If the level is elevated, treatment should be initiated with a goal of bringing the level below 50 mg/dL. In addition, the patient's other cardiovascular risk factors (including LDL levels) should be optimally managed. Apart from the total Lp(a) plasma concentration, the apo(a)

isoform might be an important risk parameter as well (Klausen *et al.*, 1997; Paultre *et al.*, 2000).

Prior studies of the relationship between LP(a) and ethnicity have shown inconsistent results. Lipoprotein (a) levels seem to differ in different populations. For example, in some African population, Lp(a) levels are, on average higher, than other groups, so that using a risk threshold of 30 mg/dl would classify up to greater than 50% of the individuals higher risk (Cobbgert *et al.* 1997: Bctaihold *et al.*, 1999; Dahlen and Ekstedt, 2001: Schmidt *et al.*, 2006). Some part of this complexity may be related to the different genetic factors involved in determining Lp(a) levels. One recent study showed that in different ethnic groups, different genetic alterations were associated with increased Lp(a) levels (Dumitrescu *et al.*, 2011).

More recent data suggest that prior studies were under-powered. The Atherosclerosis Risk in Communities (ARIC) followed 3467 African Americans and 9851 whites for 20 years. The researchers found that an elevated Lp(a) conferred the same risk in each group. However,African Americans had roughly three times the level of Lp(a), and Lp(a) also predicted an increased risk of stroke (Virani *et al.*, 2012).

Approximate levels of risk are indicated by the results below, although at present there are a variety of different methods by which Lp(a) is measured.

A standardized international reference material has been developed and is accepted by the WHO Expert Committee on Biological. Standardization and the International Federation of Clinical Chemistry and Laboratory Medicine. Although further standardization is still needed, development of a reference material is an importance step towards standardizing results (Dad *et al.*,2004: Marcovina *et al*, 2004). Lipoprotein(a) - Lp(a) Desirable: < 14 mg/dL (< 35nmol/1) Borderline risk: 14 - 30 mg/dL (35-75 nmol/1) High risk: 31-50 mg/dL (75 -125 nmol/1) Very high risk: > 50 mg/dL (> 125 nmol/1) LP(a) appears with different isoforms (per kringle repeats) of apolipoprotein - 40% of the variation in Lp(a) levels when measured in mg/dl can be attributed to different isoforms. Lighter Lp(a) are also associated with disease. Thus a test with simple quantitative results may not provide a complete assessment of risk (Boerwinkle *et al.*, 1989; Ryan *et al.*, 2005).

Treatment

Currently, the recommended treatment for an elevated lipoprotein A is niacin, 1-3 grams daily,

generally in an extended release form. Niacin therapy can reduce lipoprotein A levels by 20-30%. Aspirin may be beneficial as well. A recent meta-analysis suggests that atorvastatin may also lower Lp(a) levels (Takagi and Umemoto, 2012). In severe cases, such as familial hypercholesterolemia, or treatment resistant hypercholesterolemia, lipid apheresis may result in dramatic reductions of lipoprotein A. The goal of treatment is to reduce levels to below 50 mg dL. (Nordestaaard *et aL.*,2010).

Other medications that are in various stages of development include thyromimetics, cholesterol-ester- transfer protein (CETP inhibitors),anti-sense oligonucleopeptides, and proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors. L-carnitine may also reduce lipoprotein a levels (Nordestaaard *et aL.*, 2010).

Gingko biloba may be beneficial, but has not been clinically verified. Coenzyme Q-10 and pine bark extract have been suggested as beneficial, but neither has been proven in clinical trials (Rodriguez *et al.*, 2007; Drieling *et aL.*, 2010; Lee *et al.*, 2011).

The effect of estrogen on lipoprotein A levels is controversial. Estrogen replacement therapy in post-menopausal women appears to be associated with lower lipoprotein A levels. However one large study suggested that there was a decreased association between lipoprotein A levels and risk. In other words, it is unclear what a high lipoprotein A level means in a woman on estrogen therapy (Suk *et al.*,2008). Estrogen as a prevention strategy for heart disease is current topic of much research and debate. Risks and benefits may need to be considered for each individual. At present, estrogen is not indicated for treatment of elevated lipoprotein A (Harman *et al.*, 2011). Tamoxifen and raloxifen have not been shown to reduce levels.

The American Association of Pediatrics now recommends that all children be screened for cholesterol between the ages of 9 and 11. Lipoprotein A levels should be considered particularly in children with a family history of early heart disease or hypercholesterolemia. Unfortunately, there have not been enough studies to determine which therapies might be beneficial (EPIG, 2011).

Lipid Tetrad Index

Lipid tetrad index is derived by the product of cholesterol, triglycerides and Lipoprotein A values divided by the HDL level. It may be the best estimate of the total burden of dyslipidaemia as it eliminates the need for various cut-off points and ratios involving the lipid

subsets. A high index (greater than 20,000) would indicate the presence of a highly atherogenic lipid profile. This index can serve as a better and novel risk factor for CAD as has been determined in a few studies (Rajappa *et al.*, 2006). There is insufficient data on lipid levels from India in patients with CAD; only a few studies have been performed in North India (Goel *et al.*, 2003). Therefore the study was planned to evaluate the relative sensitivity and specificity of the lipid subsets as risk factors in the prediction of coronary events and to evaluate the lipid tetrad index as a potential predictor of CAD.

The current work is aimed at evaluating C-reactive protein, Selenium.Glycosylated haemoglobin, and Lipoprotein A of Diabetic patients attending metabolic clinic in the Federal Medical Centre Owerri, Imo State.

MATERIALS AND METHODS

Study Area

The study was conducted at the Federal Medical Centre (F.M.C), Owerri. Owerri is the capital of Imo state, South-East Nigeria, and it consists of three (3) local government areas; Owerri West, Owerri North, and Owerri Municipal, which cover an area of approximately 40 square miles (100km^2). It provides home for a population of 127,213 people of mainly Igbo ethnic group and non-indigenes, made up of 62,990 males and 64,223 females (N.P.C, 2006). Owerri lies within latitudes 5°25' and 5°29' and longitudes 6°59' and 7°3'E.

The study protocol was reviewed and approved by the F.M.C ethical committee.

Study Population

A total of 200 subjects were used for the study. These included; 120 patients (55 males and 65 females) who attended metabolic clinic, and 80 (40 males and 40 females) healthy volunteers as control. All the subjects were in the age group of 20 to 60 years.

Selection Criteria

(A) Inclusion Criteria

Diabetes mellitus patients of either sex in the age group of 20 to 60 years.

Patients with new cases of diabetes mellitus confirmed by an Oral Glucose Tolerance Test (OGTT) and Glycosylated haemoglobin (HbAic) of 7% and above.

(B) Exclusion Criteria

Individuals with tasting venous plasma glucose concentration of not

more than 6.3 mmol/L and HbAic of not more than 4.5%.

Patients suffering from active liver disease.

Patients suffering from other associated diseases. Pregnant and lactating female patients. FflV-positive diabetic patients.

Patients who did not indicate interest in the study.

(C) Selection of Control Apparently healthy volunteers of both sexes in the age group of 20-60 years.

Sample Collection

With a sterile syringe, 5ml of blood was collected from each subject from the ante-cubital vein using the standard venepuncture technique between 9am and 11am. 2ml and 3ml of the blood sample were dispensed into sodium fluoride-oxalate and lithium-heparin anticoagulant tubes respectively and mixed. The samples were centrifuged at 3000rpm for 5 minutes to separate the serum.

The Serum obtained was stored at -prior to use **for** estimation of lipid profiles.

Laboratory Procedures

All reagents and kits were commercially prepared and the manufacturers' standard operating procedures (SOP) were strictly followed.

(A) Lipid Estimation (i) Cholesterol Estimation Method: Direct Method as used by Agappe (Remaley, 2012). Cholesterol reagent manufactured by Agappe Diagnostics, Switzerland, LOT number 51204002 was used.

Principle As Modified By Agappe Laboratories

The enzymatic colorimetric determination of total cholesterol is based on the following reaction.

$$\text{Cholesterol ester} + H_2O \xrightarrow{\text{Cholesterol esterase}} \text{Cholesterol} + \text{Fatty acids}$$

$$\text{Cholesterol ester} + O_2 \xrightarrow{\text{Cholesterol esterase}} \text{*-4-Cholesten-3-one} + H_2O$$

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Peroxidase

$2H_2O_2$ + Phenol 4- Aminoantipyrine — quinone + $4H_2O$

(ii) Triglyceride Estimation Method: Direct Method as used by Agappe (Remaley, 2012).

Triglyceride reagent manufactured by Agappe diagnostics. Switzerland, LOT number 51410002 was used.

Principle

The enzymatic determination of triglyceride is based on the following reactions

Lipoprotein lipase

Triglyceride + H_2O

-*-Glycerol + Fatty acidglycerol kinase

Glycerol + ATP —

——»Glycerol-3-Phosphate + ADP

TDT ++

Mg

GPO

Glycerol-3-Phosphate + O_2 ————^Dihydroxyacetone phosphate + H_2O_2

POD

$2H_2O_2$+ 4-Aminoantipyrine + TOPS ————————> Violet coloured complex.

(iii) Estimation of HDL *I-'*- Cholesterol $_r$

Method: Direct Method as used by Agappe (Remaley, 2012). Agappe Diagnostics reagent for HDL-cholesterol, LOT number 51010001 was used.

Principle

The chylomicrons, VLDL, and LDL phosphotungstic acid and magnesium ions. After centrifugation, HDLs are n the supernatant. The HDL content of the is measured by an method. Estimation of LDL-Cholesterol LDL-cholesterolwas mathematically determined using Fri cholesterol - HDL-(Triglyceride/5) (Westgard *et al*, 1974).

(B) Estimation of Lipoprotein A (Lp-a) (Kamstrup *et al*, 2008)

Undiluted serum was stored at -70°C and quantitative estimation of Lp-a was done by ELISA kits

supplied by Innogenetics, Belgium. .*!

Principle Lipoprotein (a) is a one-step sandwich ELISA. The test wells of the ELISA test strips are coated with specific, polyclonal anti-apo(a) antibodies. In a first incubation step diluted samples are incubated together with the conjugate (sample incubation). The conjugate consists of a specific, monovalent antiapo(a) Fab-fragment coupled with peroxidase (anti-apo(a) peroxidase conjugate). During the incubation time the Lp(a) particles are bound to the solid phase and simultaneously marked by the conjugate. Unspecific serum components and unbound conjugate are removed by washing. In a second incubation step (substrate reaction) the enzyme reaction takes place. The peroxidase is part of the conjugate and oxidizes the substrate tetramethylbenzidine (TMB) to a blue coloured substance. To stop the reaction sulphuric acid is added and the colour changes to yellow. The colour intensity is directly proportional to the Lp(a) concentration in the sample. Optical density is measured at a wavelength of 450 nm by means of an ELISA reader. The Lp(a) concentration in the sample is quantitatively determined from the reference curve, which is run at the same time (Kamstrup *et al*, 2008). Reference Range: Normal values: 0.14-0.24 mmol/L Elevated risk/boundary: 0.25-0.35 mmol/L Pathologic values: >0.35 mmol/L.

(C) Lipid Tetrad Index

The Lipid Tetrad Index (LTI) was calculated by the product of total cholesterol, triglycerides (TG), and lipoprotein A (LP (a)) values divided by the high density lipoprotein cholesterol (HDL) levels (Buchman and Bardeen, 2003).

Lipid Tetrad Index (LTI) = Total Chol XT Gs XLP-a

Statistics Analysis

Statistics aanalysis was performed on statistics package for social science (SPSS) Windows version 20.0. Test of significance wa determined using te student's t-test the statistical significance was at $p<0.05$. The results were and the statistical significance was expressed as the Mean ± SD.

RESULTS

Table 1: Values of lipoprotein A (mmol/L) and the lipid tetrad index of the test and control subjects expressed in Mean ± Standard deviation.

Parameters Test	**Control**	**t-cal**	**t-critical**	**p-value**	**Inference**	**Lipid Tetrad Index** (LTI)

1.	0.27±0.03	0.17±0.03	4.885	1.973	p<0.05	Significant
2.	1.79±0.82	0.49±0.24	3.566	1.973	p<0.05	Significant

Table 1 shows the mean and standard deviation values of lipoprotein A (mmol/L) and the lipid tetrad index of the test and control subjects.

There was a significant difference (p<0.05) in the lipoprotein A values of the test group (0.27±0.03) when compared to the control subjects (0.17±0.03), and a consequent increase in the lipid tetrad index (1.79±0.82) compared to (0.49±0.24) in the control subjects.

Table 2: Values of lipoprotein A (mmol/L) and the lipid tetrad index of the test and control subjects with respect to age (years), expressed in-Mean ± Standard deviation.

Parameters	Test (20-40)yrs	Test (41-60)yrs	Control (20-40)yrs	Control (41-60)yrs	p-value
Lipoprotein A (mmol/L)	0.25±0.11	0.29±0.05	0.19±0.12	0.21±0.10	N/S
Lipid Tetrad Index (LTI)	1.83±0.82	1.90±0.77	0.44±0.24	0.38±0.30	N/S

S=Non Significant

Table 2 shows the mean and standard deviation values of lipoprotein A (mmol/L) and the lipid tetrad index of the test and control subjects with respect to age. There were no statistically significant differences between the ages.

Table 3: Values of lipoprotein A (mmol/L) and the lipid tetrad index of the test and control subjects with respect to gender (males/females), expressed in Mean ± Standard deviation.

Parameters	Test (males)	Test (females)	Control (males)	Control (females)	p-vaiue
Lipoprotein A (mmol/L) -	0.26±0.05	0.28±0.01	0.21±0.14	0.19±0.12	N/S
Lipid Tetrad Index (LTI)	1.81±0.82	1.78±0.87	0.46±0.27	0.48±0.26	N/S

N/S=Non Significant

Table 3 shows the mean and standard deviation values of lipoprotein A (mmol/L) and the ipid tetrad index of the test and control subjects with respect to the gender of the subjects. There were no statistically significant differences between the males and the females.

DISCUSSION

The result of this present study which evaluated lipoprotein A in a selected population of diabetics showed significantly elevated ($p<0.05$) values of lipoprotein A in the test subjects as compared to controls. However, lipoprotein A levels in this present study test group with diabetes mellitus as well as controls were much less than those observed in some of the Southern Indian studies by Mohan *et al* and Ramachandran *et al* al in 2001. This difference could be attributed to the different dietary habits; with saturated fat being the main cooking medium in the South Indian. Nevertheless, the increase in the lipoprotein A of the test subjects, in this present study raises the probability of a predisposition to the development of coronary artery disease in the test subjects. This is in consonance with the report of Gouni-Berthold and Berthold (2011), which says that Lp(a) transports the more atherogenic proinflammatory oxidized phospholipids which attract inflammatory cells to vessel walls, and leads to smooth muscle cell proliferation. Kratzin *et al.* (1987), also reported apolipoprotein (a) as sharing at least 75% homology with plasminogen including domains of plasminogen, referred to as kringle 4. 5. and pcotease domains. And that, the presence of elevated of lipoprotein A in the mimics, competes, and so interferes with the production of plasminogen which acts to digest fibrin clots after conversion to plasmin. This could thus, facilitate coronary vessel occlusion and the development of coronary artery disease.Furthermore, because Lp(a) stimulates secretion of PAI-1, it could enhance thrombogenesis. According to Sotiriou *et al* (2006), Lp(a) also carries cholesterol and thus contributes to artherosclerosis.

The effect of lipoprotein A on the atherogenicity is not additive but multiplicative which is well demonstrated by the lipid tetrad index. The mean lipid tetrad index of the test was significantly higher than the controls as has been reported earlier in the study done by Yeolekar in (2010), which reported that Asians had a deadly lipid tetrad index which becomes the single predictor of coronary artery disease in diabetes mellitus patients In accordance with the findings of Cabarkapa *et al.* (2013) which reported that there was no proportionate correlation between sex and age with the lipid profile of diabetics, this present study did not detect an association between lipoprotein A with the gender (male/female) and age of the subjects.

CONCLUSION

The levels of lipoprotein A, and the lipid tetrad index pattern of the diabetic population under study were significantly raised ($p<0.05$). Nevertheless, these changes did not appear to be dependent on the gender and age of the population under study.

Diabetes mellitus is characterized by abnormalities in lipid metabolism and inflammatory reactions which must be prevented or otherwise monitored and managed adequately if longevity is anticipated. In this present study, serum lipoprotein A levels, and lipid - tetrad index have been shown to play a key role as predictive indices in the development of coronary artery disease in diabetes mellitus.

In view of the foregoing, it is suggested that the evaluation of lipoprotein A be included as a routine in the management of diabetes mellitus.

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