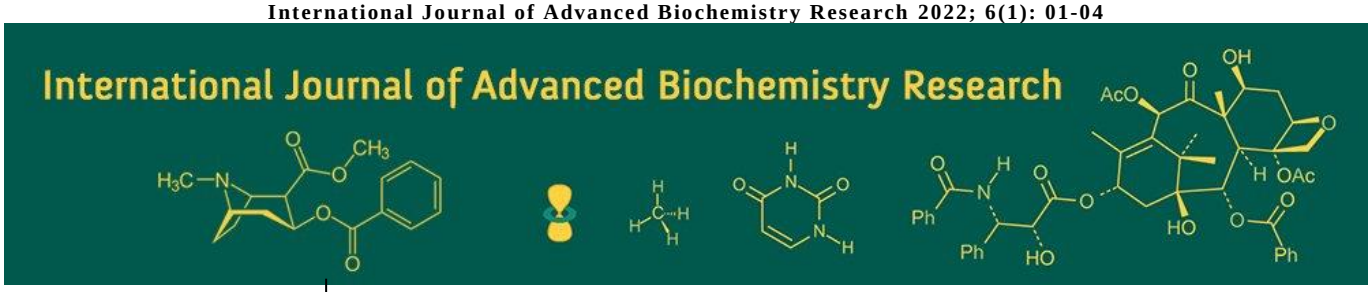

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Okoro I Ngozi
Department of Chemical Pathology, Enugu State University of Technology, Nigeria

Otobo D Daniel
College of Medicine and Health Sciences, Bingham University, Nigeria

Corresponding Author:
Okoro I Ngozi
Department of Chemical Pathology, Enugu State University of Technology, Nigeria

Pattern of Dyslipidemia, lipid free radicals and antioxidant activities in women with polycystic ovarian syndrome in Nigeria: A systematic review

Okoro I Ngozi and Otobo D Daniel

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Abstract
Aim: The aim of this study is to understand the pattern of dyslipidemia, lipid radicals and antioxidant activities in women with the polycystic ovarian syndrome in reproductive-aged Nigerian women.
Methodology: Original randomized case-control studies assessing the comparative studies of lipid patterns and panels in women with PCOS in Nigeria published between 1st January 2019 and 31st December 2020 were identified by searching online databases, including Pub MEd, Google Scholar and Research gate, using a combination of relevant keywords; PCOS, Polycystic Ovarian Syndrome, Lipid, Panel and Nigeria.
Results: LDL-C and TC show a significant increase in women with PCOS when compared to women who do not have PCOS. Amongst these women with PCOS, this panel is higher amongst those who are obese (>25 kg/m^2). The TG and HDL-C levels do not show any significant variations. However, the HDL-C levels are lower in obese women with PCOS. There is an increase in lipid product radical MDA, and a decrease in SOD and TAC. However, no variation in the GSH Px activity.
Conclusion: TG and HDL-C panels alone are not recommended parameters for the assessment and monitoring of insulin resistance in women with PCOS. TG/HDL-C, TC/HDL-C and LDL-C/HDL-C were more specific and sensitive surrogate markers.

Keywords: PCOS, polycystic ovary/ovarian syndrome, Nigeria, lipids, antioxidant, radicals

Introduction
Polycystic Ovarian Syndrome (PCOS) is a cumulation of symptoms and signs that is a result of hormonal abnormalities and results in a cascade of systemic and reproductive problems, such as anovulatory infertility. It is a problem for reproductive aged women [1]. It has a multisystemic reach that affects the menses, fertility and reproductive life of these women [2, 3].

Though a global menace, the cause of PCOS has not yet been found, however, it has been linked to Insulin Resistance [4]. This insulin resistance gives rise to dyslipidemia and other metabolic abnormalities. Dyslipidemia is a common finding in women with PCOS, with multiple causations and not just insulin resistance alone [5]. In fact, these lipid abnormalities may reflect underlying insulin resistance [6]. Thus, creating a cycle of insulin resistance causing dyslipidemia and lipid abnormalities causing more resistance. The effect of insulin resistance in these women is in lipolysis and hyperinsulinism. This leads to a cascade of events that begets the insulin resistance syndrome. This predisposes the women to diseases associated with hyperglycemia and more cardiovascular risks [5, 7].

Insulin Resistance (IR), is a common occurrence in about 50-80% of women with PCOS [5]. The reasons for it skipping some have not yet been fully understood. With IR comes lipolysis and free fatty acids. In those IR it occurs, there is an increased level of Triglycerides (TGs). This has been linked to the relocation of non-esterified free fatty acids from adipose and muscle tissues to the liver [8]. Hence, Dyslipidemia is thus defined by the presence of increased TGs and lower levels of High-Density Lipoprotein Cholesterol (HDL-C) [5].

Furthermore, the pathologies associated with rampant lipolysis and fatty acid migrations can also lead to oxidative stress. This can occur when there is a negative shift in the generation of free radicals and the production of antioxidants by the human body [9]. In women with PCOS, there is no increase in the activities of antioxidants such as Superoxide Dismutase (SOD) and

Glutathione Peroxidase (GSH Px), however, studies have shown that there is an increase in the production of free radicals. Such as MDA and Hydroxyl radicals produced from lipid peroxidation in dyslipidemia [10-13].

Hence, in the quest to understand, monitor and assess the insulin resistance syndrome researchers have tried to search for a surrogate marker that can be readily applied to the clinical management of patients as the ones available are often used in the laboratory and special tests [14]. Several markers have been proposed, however, the ones with some hope of promise are those from the lipoprotein cholesterol variants and TGs. Even amongst these groups, there are variations in specificity and sensitivity. Hence, a research gap exists in knowing exactly which parameters amongst the lipoprotein lipases to test and monitor in the assessment, diagnosis, treatment and management of dyslipidemia and Insulin Resistance in women with PCOS. However, the there are very few studies in our setting that have assessed the relationship between PCOS, oxidative stress and lipid profiles in Nigeria. One, to the best of our knowledge [12].

Globally, there has been an increase in the prevalence of PCOS in women of reproductive age. PCOS accounts for millions of Disability Adjusted Life Years (DALYs) in women of reproductive age and has a global incidence of 1.22 million. An age adjusted burden of 82.44/100 000 population in 2017 [15]. In Nigeria, the cases are often under reported due to underdiagnosis. A study by Akpata *et al.* [16] at UBTH found that PCOS had a high incidence amongst women of reproductive ages who were presenting with infertility. However, the percentage incidence varied based on the criteria used for diagnosing them.

Hence, the aim of this study is to understand the pattern of dyslipidemia, lipid radicals and antioxidant activities in women with polycystic ovarian syndrome in reproductive aged Nigerian women.

Methodology

Data Source

Original randomized case control studies assessing the comparative studies of lipid patterns and panels in women with PCOS in Nigeria published within 1st January 2019 and 31st December 2020 were identified by searching online databases, including PubMed, Google Scholar and Research gate, using a combination of relevant keywords.

Keywords in search

PCOS, Polycystic Ovarian Syndrome, Lipid, Panel and Nigeria.

Inclusion Criteria

Case control studies that assessed the lipid panels and changes in the cholesterol groups.

Exclusion Criteria

Studies whose control group had any chronic co-morbidity were excluded.

Data analysis

PRISMA guidelines for systematic reviews were followed. Study heterogenicity was assessed using Cochrane Q and I^2, and publication bias was assessed using Begg's test, Egger's test and funnel plot.

Results

The search turned up a total of 544 studies, when the papers were streamlined to Nigeria, a total of 169 studies was gotten. Using the inclusion criteria of the review period, lipid and PCOS, the papers we isolated 7 studies. After exclusion of any bias, we had 3 satisfactory case control studies with a total of 87 patients.

Clinical Assessments

All studies showed a significant increase in the Body Mass Index, waist circumference and waist-hip ration.

However, amongst the women with PCOS, those who were obese (BMI > 25 kg/m^2), had higher parameters than those who were not obese (BMI <25 kg/m^2). Parameters assessed in this comparison were weight, BMI, blood pressure, and uric acid.

Lipid Panels

Lipid Panel assessed in these studies were HDL-C, TC, TGs and LDL-C.

LDL-C

There was an increase in the concentration of Low-Density Lipoprotein Cholesterol in PCOS patients. Obese women with PCOS had higher levels of LDL-C than those who were non-obese.

TC

There were higher concentrations of Total Cholesterol in PCOS patients. Obese PCOS women had higher levels of Total Cholesterol than those who were not.

TGs

No significant rise in the concentration of Triglycerides in PCOS patients. Obese women had higher levels of TGs in comparison to non-obese women. In obese women with PCOS, TG levels correlated directly with Insulin Resistance (IR).

HDL-C

No significant rise in the concentration of High-Density Lipoprotein Cholesterol in PCOS patients.

Obese patients had lower levels do HDL-C in comparison to those who were not obese.

Lipid Comparative Ratios

Ratios of 3 lipid parameters were analyzed; TC/HDL-C, TG/HDL-C and LDL-C/HDL-C. The results showed that though they were all higher in women who had PCOS, they were higher in those who were obese compared to those who were not obese.

Lipid Product Radicals

MDA: There is a significantly higher level of Malondialdehyde in women with PCOS in comparison to those who do not have PCOS.

Antioxidant Activities

SOD: When compared to women who do not have PCOS, there are lower levels of Superoxide Dismutase.

GSH Px: There is no significant difference in Glutathione Peroxidase activities between women with PCOS and those who do not have it.

TAC: There is a decline in the Total Antioxidant Capacity

amongst women who have PCOS.

Discussion

The aim of the study was to understand the pattern of dyslipidemia, lipid radicals and antioxidant activities in women with the polycystic ovarian syndrome in reproductive aged Nigerian women. This was a bit difficult seeing that there was a scanty gap in research studies analyzing the relationships between dyslipidemia, radicals and antioxidants in women with PCOS in Nigeria. In the end, we found two case-control study papers; one that had the comparative analysis that we sought and 2 others that made further analysis and inferences concerning lipid analysis and results in women with PCOS in Nigeria.

The results showed that there were obvious alterations in the lipid patterns in women who had PCOS in comparison to those who did not. These variations were not random as they had similarities amongst test groups in these different studies. There was an increase in Total Cholesterol levels and LDL-C and a decrease in HDL-C. However, unlike other studies carried out, a significant increase in TG levels in Nigerian women with PCOS was not observed. TG levels have been proposed to be a marker for insulin resistance in these studies [12, 17, 18]. Hence, this begs the question, what then will be a surrogate marker for insulin resistance in Nigerian women with PCOS?

There were variations amongst the women with PCOS, with a benchmark being obesity. The studies showed that women with PCOS who were obese had more adverse test panels and clinical variations than those who were not. Assessment of clinical and baseline cardiovascular risk factors was higher in women who had PCOS in comparison to those who did not and worse in those who were obese. Clinical parameters such as waist circumference, waist-hip ratio, body mass index, blood pressure and hip circumference.

In the clinical sense, this simply means that exercise and weight management therapies should be prioritized in women who have PCOS. Therapeutically speaking, BMI corrections and weight management has been seen to improve the reproductive outcomes of women who have PCOS, such as regular menses and fertility [19]. Furthermore, exercise will prevent the repeating cascade of Insulin Resistance associated with atherogenic lipoprotein cholesterol [LDL-C], by limiting the availability of LDL-C which will promote insulin producing cell's fatty obstruction leading to more insulin resistance.

In the biochemical management of PCOS, searching for a surrogate marker to monitor and assess the development of IR is crucial. However, from the studies so far, TG whose rise is commonly correlated with the development or progress of IR in previous studies outside Nigeria was not seen to yield satisfactorily similar results in the Nigerian studies. More studies in this field will be needed to confirm or debunk this.

Furthermore, some studies have proposed using parameters of LDL-C and TG as surrogate markers for IR [20]. While some have suggested the TG/HDL-C ratio instead [21]. But definitely not LDL-C, as we saw from our studies that a rise in LDL-C does not necessarily mean Insulin Resistance, as we saw in the discorded levels of LDL-C amongst PCOS women who were obese and those who were not obese as against their similar levels of TG. Hence, while TG may or may not be a reliable marker for IR in women with PCOS, LDL-C is mainly a reflection of their propensity to obesity, which may then have an impact on their insulin sensitivity [22].

In regards to radicals' production and antioxidant clearing, there is a pathological left shift. This is due to an increase in radicals, such as MDA that is produced during lipid peroxidation along with the hydroxyl radical. However, clearing by antioxidants are deficient as there is a decrease rather than increase in the Total Antioxidant Concentration (TAC). This thus leads to cellular stress, lysis and other subsequent associated pathologies in women with PCOS.

The shortcoming of this study was in the fact that very few research study papers comparing the impact of lipid profiles, radicals and antioxidant activities in PCOS women in our country Nigeria. Hence, definitive inferences cannot be fully made yet. Hence, this is still a very open window for research.

Conclusion

Monitoring of the lipid profiles in women with PCOS can be a good pointer to underlying insulin pathologies, such as insulin resistance and hyperinsulinemia, amongst others. While TG/HDL-C ratio and TG are internationally proclaimed lipid parameters for the assessment of insulin resistance in women with PCOS; no significant difference was seen in our environment between women who had PCOS and those who did not. Although women who were obese were observed to have lower HDL-C levels in comparison to those who were not.

More studies are needed in this Gynaeco-biochemical field in the Nigeria setting.

Abbreviations

LDL-C – Low-Density Lipoprotein Cholesterol
HDL-C – High-Density Lipoprotein Cholesterol
TGs - Triglycerides
TC – Total Cholesterol
TAC – Total Antioxidant Concentration
GSH Px – Glutathione Peroxidase
PCOS – Polycystic Ovary/Ovarian Syndrome
IR – Insulin Resistance
MDA - Malondialdehyde
SOD- Superoxide Dismutase

Conflict of Interest

The authors declare no conflict of interest in this paper.

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Role of Authors

The authors collaborated on every part of this paper together.

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