Original Research Article

Evaluation of Lipid profile and some Renal Parameters in some selected ethnic population with fat-mass and obesity-associated gene (FTO) variants in Niger Delta, Nigeria

ABSTRACT

Aim: To evaluate lipid profile and some renal parameters in some selected ethnic population with fat-mass and obesity-associated gene (FTO) variants in Niger Delta, Nigeria.
Study design: Case-controlled observational study
Place and Duration of Study: Federal Medical Centre, Asaba, Delta State and Safety Molecular Pathology Laboratory, Enugu, Nigeria, between March 2020 and February 2022.
Methodology: Changes in lipid profile and some renal parameters in FTO gene was studied in ninety-eight (98) type 2 diabetes (T2D) subjects (78 cases and 20 controls) from four different tribes in the Niger Delta region, Nigeria. Multistage sampling method was employed in the subject selection. The subjects were first separated into two groups – new cases (less than a year of diagnosis as Diabetic) and old cases (one year & above). Equal number of samples was then randomly collected from each of the cluster groups. 10mls of blood was collected into plain bottles for the assay of the above-named markers, and were assayed using spectrophotometric and ELISA methods. The data were analyzed using GraphPad Prism, version 8.0.2 and p values less than *.05* were considered statistically significant.
Results: The results showed that the Ijaw tribe had the highest mean total cholesterol (TCHOL), low density lipoproteins (LDL), Castelli Risk Ratio (CRR), atherogenic coefficient (AC) values (5.36 ± 0.99, 3.36 ± 0.87 mmol/l,3.76 ± 1.18 and 2.86 ± 1.16) respectively, which were significantly higher (*P<.05*) than those of the control group, while the Urhobo tribe had the highest mean TG and AIP values (1.47 ± 0.51 mmo/l and 0.08 ± 0.01), The control subjects had the highest mean HDL values (1.51 ± 0.49mmo/l), which were significantly higher(*P<.05*) than that of the control subjects. Mean creatinine level was highest in the control group (101.1 ± 21.24 µmol/L), while the Urhobo tribe had the highest mean MDRD levels (94.15 ±36.17 ml/min). Special diets did not contribute to any significant difference in the biochemical indices of the subjects apart from significant changes in the levels of triglyceride.
Conclusion: From the results, we conclude that the levels of lipid profile varied with the tribe for subjects with FTO variants and control subjects and only triglyceride levels are affected by specific diets.

Keywords: lipid profile, renal parameters, FTO variants, Niger Delta, Nigeria.

1. INTRODUCTION

Several studies have reported that polymorphisms within the fat-mass and obesity-associated gene (FTO) are strongly associated with obesity [1,2] and obesity is a major risk factor for type 2 diabetes (T2D) [3,4]. The pathogenesis of obesity and T2D is reportedly related to variations in the fat mass and an obesity-associated gene (*FTO*); however, as the number of reports increases, particularly with respect to varying ethnicities, there is a need to determine more precisely the natur and extent of the effect of FTO gene polymorphisms in each ethnic group. In addition, some reports have claimed ethnic-specific associations with alternative single nucleotide polymorphism (SNPs), and to that end there has been a degree of confusion [5]. Recently, genome-wide association studies (GWAS) have identified a number of genetic polymorphisms that are associated with an increased risk for obesity and T2D [6,7]. Reports of different studies in different populations or geographical locations, appears to suggest different patterns of association of FTO gene variants with obesity and T2D in varying ethnicities, and several researchers have called for more work in other ethnic populations to determine more precisely the extent of the effects in each ethnic group. In addition, some reports have claimed ethnic-specific associations with alternative SNPs, and to that end there has been a degree of inconsistency. Also, there is paucity of data available

on the FTO gene allele variants in African and Nigerian Populations. Knowing the FTO gene variants common in persons with obesity and T2D in each of the ethnic population to be studied will be adding to the knowledge available in the understanding of the etiology and pathogenesis of these disorders and may be useful in prediction and identifying the possible complications that may arise in patients with these genetic variants.

Elevated serum triglyceride levels have been associated with β-cell dysfunction and reduced insulin secretion in prediabetes [9]. Mechanistically, hypertriglyceridemia reduces glucose-induced insulin secretion through the glucose-fatty acid cycle, and promotes β-cell apoptosis by stimulating the production of ceramide and nitric oxide. Also, elevated triglyceride levels can cause lipotoxicity by accumulating within pancreatic β cells [9]. Cholesteryl ester transfer protein mediates the exchange of lipids from Triglyceride-rich lipoproteins with high-density lipoprotein (HDL). Increased Triglyceride levels in insulin-resistant states accelerate this exchange. Then, the Triglyceride in HDL cholesterol (HDL-C) is hydrolysed by hepatic lipase, resulting in smaller HDL-C particles. ATP-binding cassette transporter A (ABCA1) mediates the efflux of cholesterol to small HDL3 particles. Subjects with prediabetes have significantly increased levels of small HDL3 particles compared with HDL-C levels. The proportion of small HDL3 particles is positively associated with Triglyceride and negatively associated with HDL-C. In contrast to Triglyceride, HDL-C promotes insulin secretion through its interaction with ABCA1. Low HDL-C concentrations may also lead to progression to diabetes from prediabetes. However, it is unclear if HDL-C levels are associated with β-cell dysfunction.

The increasing frequency of cardiovascular disease (CVD) rests on the presence of major cardiovascular risk factors including dyslipidemia. This dyslipidemia is also a target for the prevention and treatment of many cardiovascular diseases. Hence, identification of individuals at risk of CVD is needed for early identification and prevention [10]. Dyslipidemia is a single strong risk factor for the development of future cardiovascular events in the population such as stroke, coronary heart disease, myocardial infarction, and peripheral vascular disease [11]. It has been described as a disease of the economically advanced societies, but in recent times, it has been discovered to find its way into the semi-urban societies among its dwellers, who are at the increasing risk of developing future cardiovascular events [12]. Hence, early identification and diagnosis of dyslipidemia at its earliest stage before the onset of cardiovascular events among this populace is a worthwhile cardiovascular preventive measure [13].

In the evaluation of dyslipidemia, triglycerides (TGs), low-density lipoproteins-cholesterol (LDL-C), high-density lipoproteins-cholesterol (HDL-C), and total cholesterol (TC) are the lipid profiles that are commonly considered, with emphasis majorly on LDL-C as “bad lipoprotein [10]. Using either LDL-C alone or HDL-C alone is inadequate for the prediction of cardiovascular risk, especially in individuals with intermediate risk [14].

One of them is Cardiac Risk Ratio (CRR) which is frequently used for risk assessment of cardiovascular disease (CVD) and is given by the total cholesterol to HDL cholesterol ratio [15]. Another index is Atherogenic Index of Plasma (AIP), calculated as log (TG/HDL-C). AIP is considered to be a good predictor of atherosclerosis [16] and a highly sensitive predictor of risk for CVD. AIP values show substantial agreement with the results of coronary angiography [17] and are used to predict acute coronary events [17] and prognosis in patients with acute myocardial infarction [18]. Atherogenic Coefficient (AC) is another index which is given by the ratio of non-HDL cholesterol to HDL cholesterol. Non-HDL-C is easily calculated, with no need for previous fasting of the patient. It is essentially the cholesterol analogue to an Apo B level, having a higher correlation coefficient in comparison with the LDL cholesterol concentration [19]. In developed countries, atherosclerosis is the major cause of death and premature disability and is predicted to become the leading global cause of total disease burden by the year 2020 [20].

The Modification of Diet in Renal Disease (MDRD) Study equation was developed to estimate glomerular filtration rate (GFR) from age, sex and race, and serum levels of creatinine, urea and albumin; a simplified four-variable form of the equation, which dispenses with the need for urea and albumin measurements, was subsequently formulated. The clinical utility of GFR estimates derived from these and other equations is compromised by the use of different creatinine assays in different laboratories. In response to an initiative implemented by the National Kidney Disease Education Program for creatinine standardization across the US, MDRD equations were recently revised and revalidated (Levey *et al.* 2006). Levey *et al*. compared the revised MDRD equations with the Cockcroft–Gault equation, using data from the original MDRD study population of 1,628 patients with chronic kidney disease. GFR measured as urinary clearance of ^{125}I-iothalamate was used as a reference standard. The percentage of GFR estimates within 30% of measured GFR was 90% for the four-variable MDRD equation, 91% for the six-

variable MDRD equation and 83% for the Cockcroft–Gault equation. Estimates derived from any of the equations were less accurate when measured GFR exceeded 60 ml/min/1.73 m^2. The simplicity of the four-variable MDRD equation and its comparable performance to its six-variable predecessor made it a useful and reasonably reliable tool for estimating GFR in patients with chronic kidney disease with the US standardization of serum creatinine measurement in 2008 [27].

The aim of this study was to evaluate lipid profile and some renal parameters in some selected ethnic population with fat-mass and obesity-associated gene (FTO) variants in Niger Delta, Nigeria.

2. MATERIALS AND METHODS

2.1 Study Area

The study was carried out in Niger Delta region of Nigeria, with Federal Medical Centre, Asaba serving as the major point of the sample collection and some analysis. Some samples were also collected at Agbor & Bomadi. The Igbo participants were drawn from the Igbos of Delta State, Rivers State and Imo State; the Ijaw participants were drawn from the Ijaws of Delta State, Bayelsa State and Rivers State.

The Niger Delta was once known as the Oil Rivers, Nigeria's Niger Delta region is a very densely populated region, a major palm oil producer. After its expansion, it became the Niger Coast Protectorate. Stretching directly on the Gulf of Guinea on the Atlantic Ocean in Nigeria, the Niger Delta used to be historically made up of present-day Bayelsa, Rivers, and Delta states are today, made up of nine coastal states. The federal government of Nigeria's current definition states that the delta extends over about seventy thousand km^2 and makes up almost 7 percent of its landmass. The Niger Delta comprises of level low lying muggy landscape that is befuddled by wandering and anastomosing streams, waterways and brooks [21].

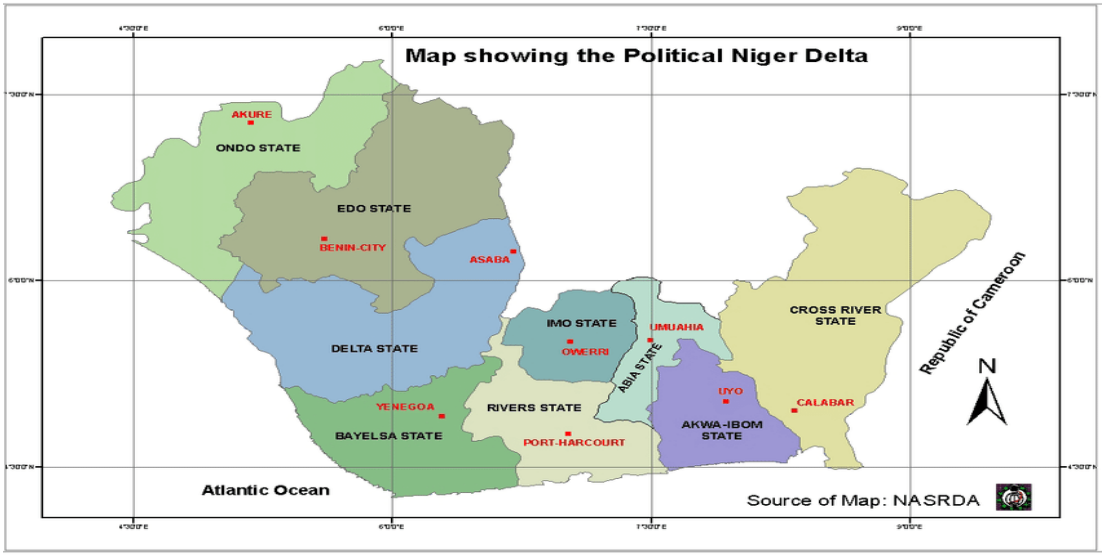

Figure 1: Political Map of the Niger Delta Area.

Asaba, the capital city of Delta State, Nigeria is situated within geographical co-ordinates 6°11′52.23″N6°43′42.48″E. It is situated on a terrace of the lower Niger River, overlooking the point where the Anambra River flows into it. Beyond the river banks, on the high plains which are far more extensive than the river basins, secondary forest vegetation flourishes.

2.2 Research Design

This is a case-controlled observational study involving the association between FTO gene allele variants and HbA1c, Fasting blood sugar, Insulin, C-Peptides, Adiponectin and HOMA-IR in obese/T2D subjects from selected ethnic groups in Niger Delta, Nigeria. The bio-data and medical history of the subjects was obtained using questionnaire, measuring their weight with a calibrated weighing scale, height and waist circumference.

2.3 Sample Size

A total of 98 subjects enrolled for this study. Sample size calculated based on the method of Allain et al. [22].

2.4 Sampling Method

Multistage sampling method was employed in the subject selection. The subjects were first separated into two groups – new cases (less than a year of diagnosis as Diabetic) and old cases (one year & above). Equal number of samples was then randomly collected from each of the cluster groups.

2.5 Selection Criteria

2.5.1 Inclusion Criteria

Individuals who are purebred of the selected tribes in Niger Delta, aged at least 21 years diagnosed with T2D for at least one year. Controls: Individuals who are from the selected tribes with no history of diabetes, and a fasting blood glucose of less than 6.5mmol/l. The cluster groups were considered also.

2.5.2 Exclusion Criteria

Individuals not of the selected tribes, those who are not purebred from the selected tribes, those who are critically ill subjects and female participants who are pregnancy.

2.6 Sample Collection and Analysis

2.6.1 Sample Collection

Ten millilitres (10ml) of blood were randomly collected from 19-20 subjects from each of the selected tribes following the sampling methodology described earlier and 20 control made of 5 non-diabetic, non-obese subjects from each of the selected tribes. This was after completing the questionnaire and signing the consent form. Their body weight in kilogram, height in meter and waist circumference in centimeter was also measured and recorded. 4.0ml into vacutainer type plain tubes. The sample was allowed to retract, then centrifuged at 3000rpm for 5 minutes. The serum was separated into a cryotubes for the assay of lipid profile and creatinine levels.

2.6.2 Sample Analysis

2.6.2.1 Serum Total Cholesterol

Serum fasting cholesterol was performed by the cholesterol oxidase-peroxidase, enzymatic endpoint method using Erba chem v5 semi-autoanalyzer and kit from Randox [22].

2.6.2.2 Serum Triglyceride

Serum fasting Triglyceride was performed by a modified enzymatic colourimetric method using Erba Chem v5 semi-auto analyzer and kit from Randox [23].

2.6.2.3 Serum HDL-Cholesterol

Quantitative in vitro determination of HDL-Cholesterol in serum was performed using phosphotungstic acid precipitation and the cholesterol oxidase-peroxidase method [24].

2.6.2.4 Serum LDL-Cholesterol

Quantitative in vitro determination of HDL-Cholesterol in serum was performed using Polyvinyl Sulphate/Polyethyleneglcol precipitation and the cholesterol oxidase-peroxidase method [25].

2.6.2.5 Atherogenic Indices

Atherogenic indices [Atherogenic Index of Plasma (AIP), Cardiac Risk Ratio (CRR) and Atherogenic Coefficient (AC)] were calculated by using the values of lipid profile parameters in the following way:

AIP = Log (TG/HDL-C)

Where, concentration of TG and HDL are in mmol/L.

Calculation of AIP was done using CZECH online calculator of atherogenic risk.

CRR = TC/HDL-C

AC = (TC-HDL-C)/HDL-C

2.5.2.6 Serum Creatinine

Serum Creatinine was performed by alkaline-picric acid Kinetic method using Erba chem v5 semi-auto analyzer and kit from Randox [26].

2.6.2.7 Modification of Diet in Renal Disease (MDRD)

Modification of Diet in Renal Disease (MDRD) was calculated using the equation by Levey et al. [27].

eGFR = 175 x $(S_{cr})^{-1.154}$ x $(Age)^{-0.203}$ x 0.742 [if female] x 1.212 [if Black] for creatinine in mg/dl or eGFR = 30849 x $(S_{cr})^{-1.154}$ x $(Age)^{-0.203}$ x 0.742 [if female] x 1.212 [if Black] for creatinine values in *u*mol/l

eGFR - Extimated Glomerular filtration Rate, S_{cr} – Serum Creatinine

2.6 Statistical Analysis

The data were analyzed using GraphPad Prism, version 8.0.2, (California, USA). Quantitative variables were expressed as Mean (X) ± standard deviation (SD). One-Way Analysis of Variance (ANOVA) and students' statistical t-test were the inferential statistics used to observe the differences mean values, while Tukey's Post Hoc analysis was also done to observe the differences within different sub-classes. P values less than *.05* (*p<.05*) were considered statistically significant.

3. RESULTS AND DISCUSSION

Table 1: One-Way ANOVA Results of Mean±SD of Fasting Lipids Parameters, Atherogenic and Renal Indices of Subjects of Niger Delta Tribes with FTO gene variations

Parameters	Ijaw	Urhobo	Ika	Igbo	Control	F value	P value	Remark
TCHOL (mmol/L)	5.36 ± 0.99[a]	3.84 ± 0.50[b]	3.94 ± 0.84[b]	4.21 ± 0.52[b]	4.47 ± 0.60[b]	14.47	<0.0001	S
TG (mmol/L)	1.09 ± 0.33	1.47 ± 0.51	1.35 ± 0.58	1.46 ± 0.38	1.39 ± 0.53	2.033	0.0960	NS
HDL (mmol/L)	1.49 ± 0.47[a]	1.18 ± 0.27[b]	1.31 ± 0.29[a]	1.31 ± 0.25[a]	1.51 ± 0.49[a]	2.855	0.0278	S
LDL (mmol/L)	3.36 ± 0.87[a]	1.88 ± 0.51[bc]	2.03 ± 0.77[b]	2.22 ± 0.39[b]	2.45 ± 0.51[bd]	16.71	<0.0001	S
AIP	-0.15 ±-0.13[a]	0.08 ± 0.01[b]	-0.02 ± -0.01[a]	0.03 ± 0.01[b]	-0.02 ± -0.01[a]	3.792	0.0066	S
CRR	3.76 ± 1.18	3.32 ± 0.58	3.11 ± 0.83	3.29 ± 0.49	3.32 ± 0.62	1.880	0.1203	NS
AC	2.86 ± 1.16[a]	2.37 ± 0.57[a]	2.14 ± 0.83[b]	2.28 ± 0.50[a]	2.35 ± 0.61[a]	2.486	0.0486	S
Crt (µmol/L)	85.85 ± 15.5	87.25 ±22.75	99.25 ± 34.47	96.80 ±30.28	101.1 ± 21.24	1.486	0.2124	NS
MDRD (ml/min)	85.90 ±22.3	94.15 ±36.17	75.35 ± 22.51	86.90 ±32.80	80.60 ± 20.70	1.308	0.2726	NS

PostHoc (Tukey's):

Within same row, values with different superscripts (a, b), (c, d) differ significantly when various tribes were compared against each other. S=Significant, NS=Not Significant At p<0.05.

Abbreviations: *TCHOL=Total cholesterol; TG=Triglyceride; HDL=High Density Lipoprotein; LDL=Low density Lipoprotein; AIP=Atherogenic indices of Plasma; CRR= Castelli Risk Ratio; AC= Atherogenic coefficeirnt; Crt=Creatinine; MDRD=Modification of Diet in Renal Disease.*

Table 2: Comparative Results of Mean±SD of Fasting Lipids Parameters, Atherogenic and Renal Indices of Subjects of Niger Delta Tribes with FTO gene variations on Special Diet

Parameters	No special diet	Special diet	T value	P value	Remark
TCHOL (mmol/L)	4.25 ± 0.78	4.45 ± 1.12	0.968	0.335	NS
TG (mmol/L)	1.44 ± 0.56	1.22 ± 0.317	2.013	0.047	S
HDL (mmol/L)	1.28 ± 0.32	1.37 ± 0.38	1.160	0.249	NS
LDL (mmol/L)	2.28 ± 0.76	2.49 ± 0.99	1.130	0.262	NS
AIP	0.03 ± 0.02	-0.06 ± 0.18	1.653	0.102	NS
CRR	3.36 ± 0.72	3.36 ± 0.97	0.025	0.979	NS
AC	2.43 ± 0.72	2.55 ± 1.09	0.574	0.567	NS
Crt (umol/L)	89.93 ± 25.74	95.17 ± 28.33	0.864	0.389	NS

S=Significant, NS=Not Significant At p<0.05.
Abbreviations: *TCHOL=Total cholesterol; TG=Triglyceride; HDL=High Density Lipoprotein; LDL=Low density Lipoprotein; AIP=Atherogenic indices of Plasma; CRR= Castelli Risk Ratio; AC= Atherogenic coefficient; Crt=Creatinine; MDRD= Modification of Diet in Renal Disease.*

This study observed a significant difference (Table 1) in the total cholesterol, HDL, LDL, AIP, and AC between the case and control with the Ijaw group showing a significantly higher lipid values compared to the others and the control group. There was however no difference in the creatinine and MDRD. Diabetic dyslipidemia is a type of secondary dyslipidemia and plays an important role in determining the cardiovascular risk of subjects with type 2 [28]. In these patients, insulin resistance is responsible for overproduction and secretion of atherogenic very low-density lipoprotein. In addition, insulin resistance promotes the production of small dense low-density lipoprotein (LDL) and reduces high-density lipoprotein (HDL) production. Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality in diabetic patients [28]. Lipoprotein-associated phospholipase A2 (LpPLA2) is an enzyme that degrades oxidatively fragmented phospholipids and may play a role in atherogenesis [29]. Individuals with IFG have significantly decreased HDL-associated LpPLA2 (HDLLpPLA 2) activity compared with subjects with normoglycemia. Low-density lipoprotein-associated LpPLA2 may exert pro-inflammatory effects, whereas HDL-LpPLA2 may have an atheroprotective role [29]. Increased levels of small HDL3 particles and decreased activity of the anti-atherogenic HDLLpPLA 2 were found in subjects with IFG [29]. Thus, subclasses of HDL-C may play a role in the pathogenesis of prediabetes. Atherogenic index of plasma is considered to be a good predictor of atherosclerosis and a highly sensitive predictor of risk for CVD [16,17]. AIP represent a clinically convenient indicator for detection of T2D with high risk for complications and associated diseases and thus is a predictor and indicator for follow-up monitoring in the treatment of patient [30]. It has recently been proposed as a marker of plasma atherogenecity because it is increased in people at higher risk for coronary heart disease and is inversely correlated with LDL particle size. The association of TGs and HDL-C in this simple ratio theoretically reflects the balance between risk and protective lipoprotein forces, and both TGs and HDL-C are widely measured and available [17]. It is superior to other traditional assessment indexes (e.g., cardiogenic risk ratio and atherogenic coefficient) in assessing risk for CV events [31]. It is also considered to predict risk for T2DM [30]. It represents a clinically convenient indicator for detection of T2DM with high risk for complications and associated diseases, and thus is a good predictor and indicator for follow-up monitoring in the treatment of patients with high-risk type 2 diabetes [30]. Based on the finding the diabetics in this tribe are not at a high risk of both CVD and atherosclerosis.

Special diets did not contribute to any significant difference in the biochemical indices of the subjects (Table 2), except with triglyceride. Elevated serum triglyceride levels have been associated with β-cell dysfunction and reduced insulin secretion in prediabetes [9]. Mechanistically, hypertriglyceridemia reduces glucose-induced insulin secretion through the

glucose-fatty acid cycle, and promotes β-cell apoptosis by stimulating the production of ceramide and nitric oxide.

4. CONCLUSION

From the results, we conclude that the levels of lipid profile varied with the tribe for subjects with FTO variants and control subjects and only triglyceride levels are affected by specific diets. The work provides interesting information on the lipid profile and may be useful to continue with deeper studies on the effect of FTO gene polymorphisms in ethnic groups in Nigeria.

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editorial office/Chief Editor/Editorial Board members of this journal.

ETHICAL APPROVAL

Ethical approval and permission were sought and obtained from the ethical committee of Federal Medical Centre, Asaba, Delta State, Nigeria.

COMPETING INTERESTS DISCLAIMER:

AUTHORS HAVE DECLARED THAT NO COMPETING INTERESTS EXIST. THE PRODUCTS USED FOR THIS RESEARCH ARE COMMONLY AND PREDOMINANTLY USE PRODUCTS IN OUR AREA OF RESEARCH AND COUNTRY. THERE IS ABSOLUTELY NO CONFLICT OF INTEREST BETWEEN THE AUTHORS AND PRODUCERS OF THE PRODUCTS BECAUSE WE DO NOT INTEND TO USE THESE PRODUCTS AS AN AVENUE FOR ANY LITIGATION BUT FOR THE ADVANCEMENT OF KNOWLEDGE. ALSO, THE RESEARCH WAS NOT FUNDED BY THE PRODUCING COMPANY RATHER IT WAS FUNDED BY PERSONAL EFFORTS OF THE AUTHORS.

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