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Phenytoin Induced Changes in Glucose and Lipid Metabolism is Related to Increased Urate Synthesis

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Authors' contributions

This work was carried out in collaboration between all authors. Author ISE designed the study, wrote the protocol, wrote the first draft of the manuscript and managed the experimental process. Authors IFU and FEU managed the literature searches and proof read the draft. All authors read and approved the final manuscript.

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ABSTRACT

Aim: The study was to investigate the relationship of phenytoin-associated hyperuricaemia with the hyperglycaemia and dyslipidaemia caused by phenytoin administration.
Methods: Forty-two albino Wistar rats were randomly divided into six (6) groups of 7 rats each. Group 1 animals served as the control (receiving normal saline 0.50 ml). Groups 2,3,4,5 and 6 received phenytoin, phenytoin + vitamin C, phenytoin + vitamin E, phenytoin +vitamin E +vitamin C and phenytoin + allopurinol respectively. The drugs were administered once daily for four weeks by oral intubation as follows: Phenytoin: 5 mg/kg body weight of rat, vitamin C: 1.4 mg/kg body weight of rat, Vitamin E: 10 IU/kg body weight of rat and allopurinol 5mg/kg body weight of rats. Appropriate immunoassay or spectrophotometric methods were used for analysis of fasting plasma glucose, insulin, cholesterol, triglyceride and catalase activities.

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Results: Showed a significant elevation of serum uric acid following phenytoin administration (p= 0.000) that were not reversed by co-administration of antioxidant vitamins but were reduced by allopurinol administration. Serum catalase activities which were significantly depressed by phenytoin treatment were reversed by antioxidant Vitamins C, E or allopurinol. The concentration of fasting plasma glucose, insulin resistance index, total cholesterol and triglyceride were significantly increase [(59.5%: p=0.001), (87.9%: p=0.005), (35.7%: p=0.000), (34.5% p=0.027)] respectively by phenytoin administration compared to control. However, the values of these parameters were not significantly lowered by antioxidant Vitamins, but significant reduction (p=0.017) to values similar to those of normal control group were observed in the group receiving both phenytoin and allopurinol. Fasting plasma insulin levels were not significantly (16.8%: p=0.137) affected by these drug treatments. Pearson bivariate correlation analysis of data of the experimental groups and control showed significant positive correlation between uric acid and fasting plasma glucose (r=0.598, P=0.000), fasting plasma insulin (r=0.394, P=0.010), insulin resistance index (HOMAIR: r=0.551, P=0.000), total cholesterol (r=0.677, P=0.000) and triglyceride (r=0.490, P.0.001).

Conclusion: We conclude that the metabolic toxicities of phenytoin associated with impaired glucose metabolism, insulin resistance and dyslipidaemia, are related to phenytoin induced hyperuricaemia.

Keywords: Phenytoin hyperuricaemia; hyperglycaemia; dyslipidaemia; insulin resistance; allopurinol.

1. INTRODUCTION

The adverse manifestation of phenytoin, a hydration anticonvulsant drug used widely for treatment of generalized or partial seizures, of epilepsy, have been reported [1-3] to range from minor gingival, hyperplasia and mild hepatotoxic effects to severe and life threatening Steven-Johnson syndrome, toxic epidermal necrolysis and teratogenic birth defects. Metabolic derangements affecting vitamins [4], lipoproteins [5] and glucose [6] leading to tissue damage have also been observed, following phenytoin administration. The hyperglycaemic effect and impaired glucose metabolism had earlier been attributed to altered insulin production and secretion by the drug treatments [7] and/or phenytoin induced insulin insensitivity by target cells [8]. Diabetic pattern of OGTT curve was observed in an 11-year old boy receiving Phenytoin for the control of epileptic seizures. These metabolic changes (hyperglycaeina and diabetic pattern of OGTT curve) were reverted to normal four weeks after discontinuation of the drug therapy [6]. The mechanism of phenytoin – induced hyperglycaemia is currently not fully understood as some reports are advocating impaired insulin release possibly due to changes in Ca2+ flux of rat pancreatic islet [7], while others are showing that the hyperglycaemia may be due to insensitivity of peripheral cells to insulin [8].

However, the relationship between phenytoin administration and impaired glucose metabolism resulting in hyperglycaemia is being speculated to be the effects of its metabolic intermediates called areve oxides [9] on the enzymes and proteins of glucose metabolic pathways. This was based on the observation of excessive cellular production of reactive oxygen species (ROS) and depletion of reduced glutathione during phenytoin treatment [10,11]. Phenytoin is metabolized primarily to the inactive paralydroxy Phenytoin (PHHPH) by CYP2C19 and CYP2C9 via a reactive arene oxide intermediate [12,13]. The accumulation of these reactive intermediate, constitute the oxidative stress of phenytoin and had been shown to be responsible for the idiosyncratic toxicities of Phenytoin including impaired glucose metabolism.

We had earlier documented significant increase in uric acid synthesis following phenytoin administration [14] and that the phenytoin induced hyperuricaemia was not ameliorated by antioxidant vitamin administration. We suggested that phenytoin, being a known enzyme inducing drug, could have caused increase in the synthesis and activities of xanthine oxidase enzyme with a resultant increase production of uric acid and hydrogen peroxide (or superoxides).

Accumulation of uric acid in blood and increased activities of xanthine oxidize enzyme have been implicated in impaired glucose tolerance and insulin secretion [15]. Chen and his colleagues had also reported significant positive correlation between high uric acid concentration in blood and some components of metabolic syndrome

such as obesity, hypertension and dyslipidaemia in a Chinese population [16]. Increased serum uric acid have also been shown to be a marker of inflammatory conditions and a predictive marker for the risk of developing cardiovascular disease, ranal failure and cancer [17].

Uric acid as a mediator of inflammation, stimulates the production of monocyte chemoattractant, protein (MCP) IL–IB, IL-6 and TNF - α [18]. Increased circulation of these proinflammatory molecules induced by high plasma uric acid and the superoxides generated as a byproduct of its synthesis by xanthine oxidase could interfere with normal glucose metabolism and insulin function in relevant tissues including liver and adipose tissues, thus resulting in hyperglycaemia and dyslipidaemia that is seen during phenytoin therapy. This study, therefore is done to determine the effect of phenytoin on insulin and its resistance index, glucose and lipid levels; and to examine the relationship of phenytoin – induced increase in uric acid with parameters of insulin function in a rat model experiment.

2. MATERIALS AND METHODS

Albino rats of the Wistar strain (135 - 150g) were obtained from the Animal House, Department of Biochemistry in the Faculty of Basic Medical Sciences, University of Uyo, Uyo – Akwa Ibom State. The animals were kept in the experimental section of the animal house, in a well ventilated standard laboratory condition of temperature and relative humidity. The animals were fed with normal rat formular (Pfizer Livestock Co. Ltd., Aba, Nigeria). Both the experimental and control animals had free access to both rat chow and water during the experimental period. The animals were randomly divided into six (6) groups of 7 rats each. Group 1 animals served as the control and were gavaged normal saline (0.50 ml). Groups 2, 3, 4, 5 and 6 received phenytoin, phenytoin + vitamin C, phenytoin + vitamin E, phenytoin + vitamin E +vitamin C and phenytoin + allopurinol respectively.

2.1 Administration of Phenytoin and Antioxidant Vitamins

Commercially available phenytoin capsules were obtained from Parke-Davis Hoofreg; Vitamin C tablets was obtained from Emzor Pharmaceuticals (Nig) Ltd, Lagos, Nigeria, Vitamin E (soft gel) was of Viboost Healthcare Limited, India and allopurinol 100 mg tablets (Zyloric) was obtained from Aspen Pharma Trading Limited, Dublin 1, Ireland. The choice of commercial products was to reflect the condition under which these medications are administered. The drugs were administered once daily by oral intubation as follows; Phenytoin: 5 mg/kg body weight of rat, vitamin C: 1.4 miligram/kg body weight of rat, Vitamin E: 10 IU/kg body weight of rat and allopurinol 5 mg/kg body weight of rats. The treatments lasted for 4 weeks.

2.2 Collection and Preparation of Samples

The animals were anaesthetized with chloroform and sacrificed after a 10 – 12 hour fasting following guidelines of our Institutional Ethics Committee on animal studies. Blood samples were collected into fluoride/oxalate tube for glucose determination and plain sample tubes for sera preparation. The blood samples were allowed to clot at room temperature for 2 hours. Sera were separated by centrifugation at 3000 g for 5 min using bench top centrifuge (MSE Minor, England). Sera were separated into plain sample tubes and stored in the refrigerator for analysis. Glucose samples were analyzed within 6 hours of collection while serum samples were stored frozen at -20℃ until analyzes within 10 days of sample collection.

The protocols involved in this study, including ethical considerations, were examined and approved by the University of Uyo Postgraduate research review board.

2.3 Biochemical Analysis

Serum proteins, uric acid, total cholesterol, triglyceride and fasting plasma glucose were measured in serum samples spectrophotometrically, using Randox kits (Randox Laboratory Ltd., Diamond Road, Crumlin, Co. Antrim, United Kingdom, BT29 4QY). Serum catalase activity was determined by the spectrophotometric assay using Bioxytech catalase kit (OxisResearch, Foster City, U. S. A.). Serum insulin was determined by ELISA method using insulin enzyme immunoassay kit from DRG Germany. Serum total protein was analyzed using biuret method kit [19]. The absorbances of all the tests were determined using spectrophotometer (HAICH, DR 3000, Germany). Insulin resistance index (HOMA1 - IR) was calculated using the formulae:

$$\text{HOMA1} - \text{IR} = (\text{FPI} \times \text{FPG})/22{,}5$$

where FIRI is fasting plasma insulin level (μU/ml) and FPG is fasting plasma glucose level (mmol/l).

Statistical analysis was carried out by employing student's t-test and post hoc, a probability of $p < 0.05$ was considered significant. Pearson's bivariate correlation was used to assess the relationships between parameters.

3. RESULTS

The association of phenytoin treatment with alteration in the metabolism of glucose and lipid, and insulin resistance indiex of albino wistar rat were investigated to highlight possible mechanisms of phenytoin induced hyperyglycaemia and insulin resistance. Table 1 showed significant elevation of serum uric acid following phenytoin administration ($p = 0.000$). The elevated serum uric acid concentrations were not reversed by co-administration of antioxidant vitamins but were however reduced by allopurinol administration to values comparable to control. On the other hand, the activities of serum catalase which was significantly depressed by phenytoin treatment were reversed by antioxidant Vitamins C, E or allopurinol.

In Table 2, the concentration of fasting plasma glucose, estimated insulin resistance index, total cholesterol and triglyceride were significantly increase [(59.5%: p=0.001), (87.9%: p=0.005), (35.7%: p=0.000), (34.5%: p=0.027) respectively by phenytoin administration compared to control. However, the values of these parameters were not significantly lowered by antioxidant Vitamins, but significant reduction (p=0.017: 16.8% increase) to values comparable with that of normal control group were observed in the group receiving phenytoin and allopurinol in combination. Fasting plasma insulin levels were not significantly (p=0.137) affected by these drug treatments.

Pearson bivariate correlation analysis of data within the group receiving only phenytoin treatment showed strong positive correlation between uric acid concentrations and fasting plasma glucose (r=0.552, p=0.225), total cholesterol (r=0.523, p=0.229), triglyceride (r=0.573, p=0.179) and fasting plasma insulin (r =0.329, p=0.471). However, the relationships between uric acid and these parameters within the group were not significant. Data across the experimental groups and control showed (Fig. 1 A–F) significant positive correlation between uric acid and fasting plasma glucose (r=0.598, P=0.000), fasting plasma insulin (r=0.394, P=0.010), insulin resistance index (HOMAIR: r=0.551, P=0.000), total cholesterol (r=0.677, P=0.000) and triglyceride (r=0.490, P.0.001). However, a negative correlation observed between uric acid and catalase was not significant (r=0.202, P=0.199). Also, estimated insulin resistance index (HOMAIR) showed significant positive correlation with total serum cholesterol (r=0.408, P=0.007) and triglyceride (r=0.384, P=0.012).

Table 1. Uric acid levels and catalase activities of rats treated with phenytoin, antioxidant vitamins and/or allopurinol

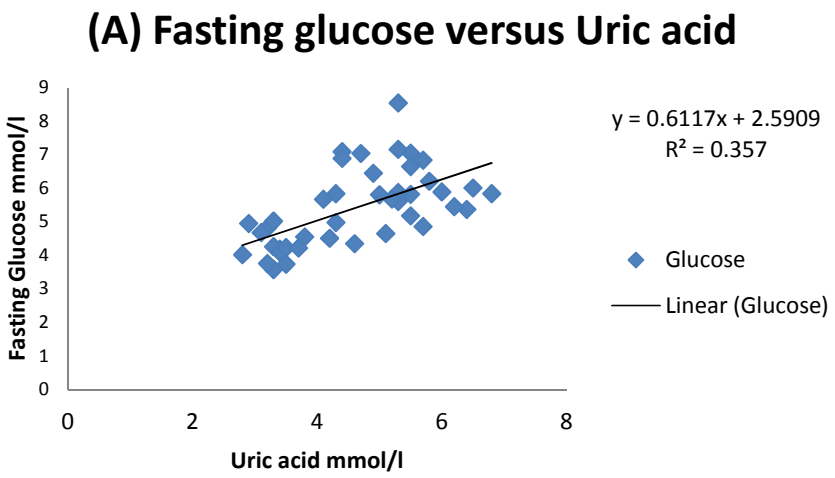
Group	Uric acid mmol/l	Cat U/mgPr	Protein g/L
1(Control)	3.37±0.11	1.63±0.11	72.71±6.43
2(Phen)	5.49±0.37*	0.97±0.10*	68.42±5.35
3(Phen+Vit C)	5.54±0.28*	2.06±0.37	70.14±4.93
4(Phen+Vit E)	5.79±1.05*	1.90±0.36	72.71±4.07
5(Phen+Vit C + Vit E)	4.79±0.49*	1.93±0.30	72.43±5.20
6(Phen+ Allopur)	3.52±0.23	1.89±0.28	72.29±4.97

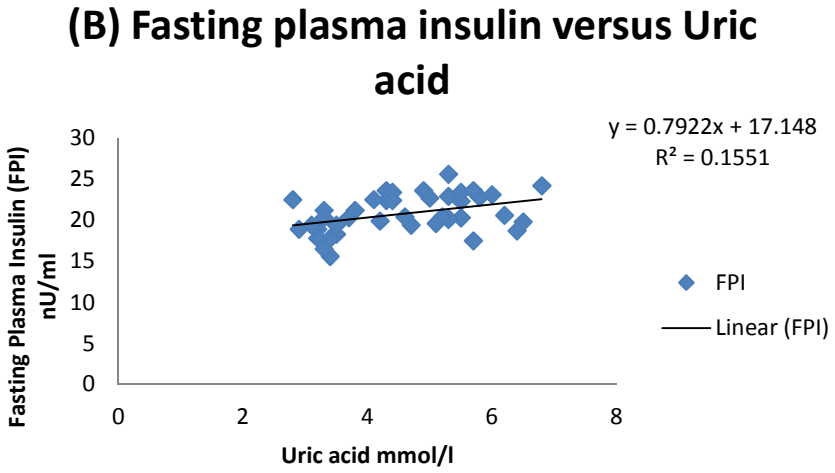
*Mean±SD. * significant difference at $p < 0.05$*

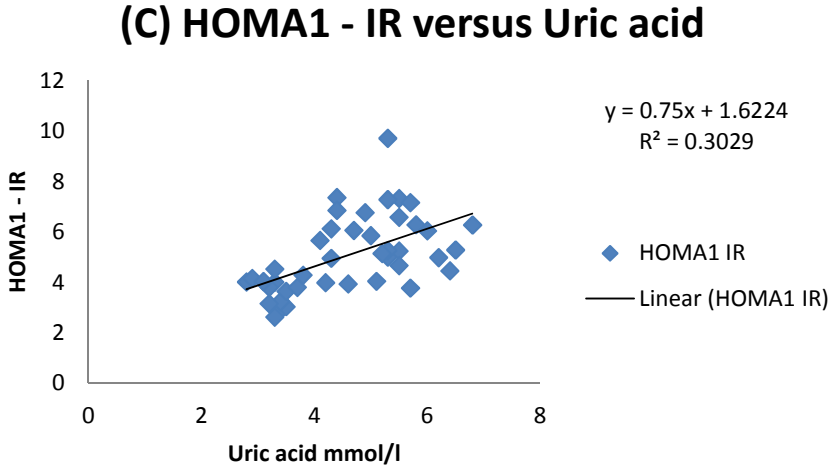
Table 2. Changes in fasting glucose, insulin and lipid levels following phenytoin treatment and in combination with antioxidant vitamins or allopurinol

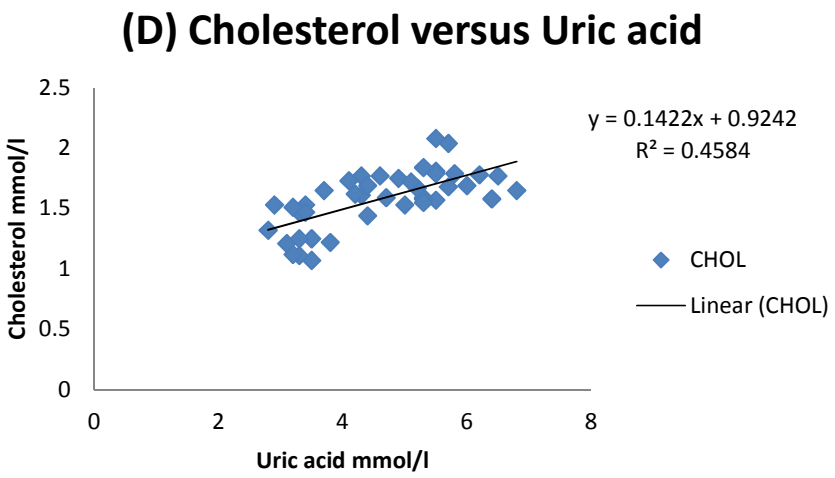
Group	FPI nU/ml	Fasting glucose mmol/l	Homair	Chol mmol/l	TG mmol/l
1(Control)	18.24±1.85	3.98±0.23	3.23±0.47	1.29±0.20	0.58±0.05
2(Phen)	21.33±2.31	6.35±0.80*	6.07±1.23*	1.75±0.16*	0.78±0.10*
3(Phen±Vit C)	21.77±2.31	5.39±0.51*	4.82±0.79*	1.69 ±0.26*	0.75±0.06*
4(Phen±Vit E)	21.84±1.88	5.63±O.57*	5.45±0.70*	1.78 ±0.09*	0.76±0.08*
5(Phen±Vit C±VitE)	21.85±2.15	5.60±0.84*	5.45±1,04*	1.55±0.09	0.67±0.12
6(Phen±Allopur)	20.05±1.54	4.61±0.84	4.09±0.89	1.35 ±0.17	0.56±0.04

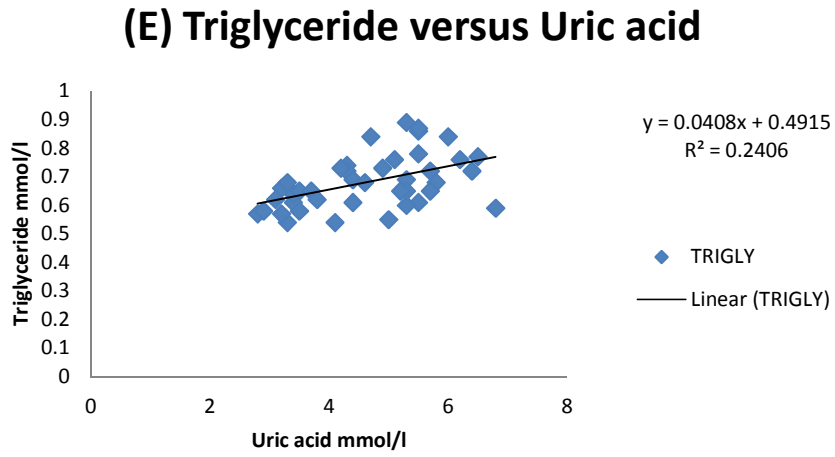
*Mean±SD. * significant difference at $p < 0.05$*


(A) Fasting glucose versus Uric acid
Fasting Glucose mmol/l
Uric acid mmol/l
y = 0.6117x + 2.5909
R² = 0.357
Glucose
Linear (Glucose)


(B) Fasting plasma insulin versus Uric acid
Fasting Plasma Insulin (FPI) nU/ml
Uric acid mmol/l
y = 0.7922x + 17.148
R² = 0.1551
FPI
Linear (FPI)


(C) HOMA1 - IR versus Uric acid
HOMA1 - IR
Uric acid mmol/l
y = 0.75x + 1.6224
R² = 0.3029
HOMA1 IR
Linear (HOMA1 IR)





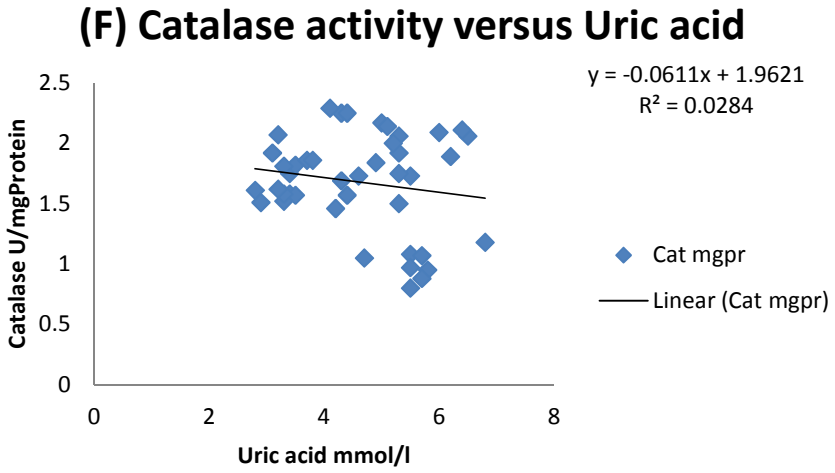


Fig. 1. Correlation graph of uric acid with fasting glucose (A), fasting plasma insulin (B), insulin resistance index HOMA1 IR (C), total cholesterol (D), triglyceride (E) and catalase activities (F)

4. DISCUSSION

The idiosyncratic effects or toxicities of phenytoin have been largely attributed to oxidative and immunological mechanisms. This study implicated elevated uric acid concentration as part of the mediators of phenytoin toxicities especially as it affects glucose metabolism and insulin function which result in chronic hyperglycaemia and dyslipidaemia. Significant increase in the serum concentration of uric acid was observed in rats following phenytoin administration and this was attributed to probable induction and/or activation of xanthine oxidase enzyme by phenytoin or its arene oxide reactive metabolites [14]. Phenytoin had been known to induce the expression of microsomal enzymes such as cytochrome P450 isoenzymes, aldehyde dehydrogenase, xanthine oxidoreductase and NADPH oxidoreductase; mainly through arylhydrocarbron receptor (AhR) or the constitutive androstene receptor (CAR) systems [20]. Also, phenytoin metabolism results in oxidative stress which enhances the activities of xanthine oxidase (but not xanthine dehydrogenase activities) and can lead to increase production of uric acid and more superoxides. It had been reported that the activities of xanthine oxidase is normally low, but its increased production of uric acid and ROS is enhanced by accumulation of intracellular ADP and NADP which are associated with oxidative stress [21,22]. The increase serum uric acid levels in phenytoin treated animals were not significantly reduced by administration of the antioxidant vitamins but allopurinol administration reduced the uric acid level to about normal control values. The inability of antioxidant vitamins to significantly reduce serum uric acid concentration to normal levels strongly support increased levels of xanthine oxidase enzyme induced by phenytoin. However, antioxidant vitamins E and C improved the level of catalase which had been depressed probably by reactive oxidant radicals arising from both phenytoin metabolism and activities of xanthine oxidase during uric acid synthesis. Antioxidant Vitamins react with the reactive oxidant radicals to prevent their damaging effects on cellular macromolecules such as proteins, lipids and DNA.

The levels of fasting plasma glucose, insulin resistance index (HOMA1- IR) and total cholesterol where also observed to increase significantly by Phenytoin treatment. These parameters which characterize metabolic syndrome were not significantly ameliorated by antioxidant Vitamin E and C administrations but were improved by allopurinol which inhibits xanthine oxidase activities. These findings strongly suggest that uric acid may also be responsible for the metabolic derangement encountered during phenytoin administration especially as inhibition of uric acid synthesis by allopurinol ameliorated the phenytoin induced metabolic changes. Co – administration of phenytoin and allopurinol significantly improved the level of catalase activity in this study presumably by preventing the formation of xanthine oxidase associated peroxides and superoxides. Combined treatment with allopurinol and phenytoin had also been shown to ameliorate ischaemic brain infarction in rats [23].

Uric acid is generally known as a plasma antioxidant molecule capable of scavenging superoxides, hydroxyl radical and singlet oxygen. It also reduces nitrosylation of tyrosine resisdues on proteins by maintaining superoxide dismutase activity [24]. These actions of uric acid are seen to be beneficial. However, uric acid itself can become a pro-oxidant (urate radical), in a setting of compromised antioxidant availability, particularly reduced ascorbic acid. It has been shown to demonstrate detrimental proinflammatory effects in adipose tissues and vascular smooth muscle cells [25] resulting in endothelial dysfunction and impaired nitric oxide generation by the endothelial cells [26]. The effects of hyperuricaemia on the adipose tissues has been said to involve increase production of monocyte Chemoattractant protein – 1 (MCP – 1), and downregulation of PPARɣ, xanthine dehydrogenase and adeponectin thus resulting ininsulin resistance, low grade inflammation and cardiovascular diseases [27]. Adipocytes from lean and healthy subjects express high levels of adiponectin, which stimulates fat oxidation, acts as an insulin sensitizer in many cell types and has antiatherogenic properties [28]. In obese subjects, adiponectin levels are decreased, and its beneficial effects are diminished [29]. Inflammatory response in the adipose tissue [30] with an increased local expression of monocyte chemotactic protein-1 (MCP-1), tumor necrosis factor-a (TNF-a), interleukin-6 (IL-6), and other proinflammatory molecules [31] are also seen in obese subjects. MCP-1 has a key role in the macrophage infiltration in the adipose tissue in obesity and development of insulin resistance [32,33]. The obesity induced imbalance in the production of adipokines contributes to insulin

resistance of the liver and muscles, impairs vascular homeostasis, and induces low-grade systemic inflammation that is critical in the development of type 2 diabetes and cardiovascular disease [34]. These effects of uric acid were shown to be mediated by MAP kinases ERK1/2 and p38 and nuclear factor-kB in a redox-dependent fashion [35].

Reports of phenytoin induced hyperglycaemia in clinical cases were documented in the literatures, but there is paucity of reports of hyperuricaemia in human studies. This discrepancy between human and rats model is not fully understood, but may be related to species differences in renaluric acid excretion and responses of the microsomal enzymes up-regulation to different chemical compounds. Rats are said to be urate-reabsorbing non-primate mammals, with a urate/anion exchanger in the brush boarder membrane of the proximal tubules, which accepts multiple monovalent organic anions, aliphatic or aromatic, including *p*-aminohippurate, as well as chloride and hydroxyl ions [36]. Such a urate/anion exchanger is absent in rabbits and pigs, which predominantly secrete urate. These species differences strongly suggest that the urate/anion exchanger is an essential mechanism for urate handling in animals. The presence of a similar urate/anion exchanger was however, demonstrated in human brush border membrane vesicles prepared from normal sections of human kidneys excised because of carcinoma but the human urate/anion exchanger showed significantly lower affinity for the aliphatic compounds lactate, β- hydroxybutyrate, and acetoacetate than those in rats [37]. These differences in uric acid handling may be responsible for the discrepancy between rats model and clinical findings.

In this study, we observed strong and significant positive correlation between uric acid and fasting plasma glucose; insulin resistance index (HOMA1 - IR), total serum triglyceride and cholesterol which support the probable involvement of uric acid in the phenytoin induced metabolic derangement of glucose and lipids. Hyperuricaemia of phenytoin treatment may therefore be incriminated in the pathogenesis of metabolic syndrome through these uric acid effects on adipocytes, liver and vascular smooth muscle cells.

5. CONCLUSION

We therefore conclude that the metabolic toxicities of phenytoin involving impaired glucose metabolism, insulin resistance and dyslipidaemia, are related to phenytoin induced increase in uric acid synthesis.

CONSENT

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist

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