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Does Anti-Gout Agent Allopurinol Affect Human Hormones Profile?

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ABSTRACT

The main objective of the prospective study is to investigate the influence of zyloric (allopurinol) drug on the human hormones profile. Sera separated from whole blood samples were withdrawn from adult males and females to measure serum FSH, E2, LH, Prolactin, Progesterone, DHEAS, Testosterone, TSH, T_3, T_4, Fasting Insulin, and Cortisol. All these hormone concentrations were determined quantitatively using ELISA procedure. The current study shows significant changes within all volunteers' hormones. We concluded that the present study may be useful in drug dose optimization depending on the drug effect on each human hormone and in the addition of new medical guidelines for drug companies to avoid negative side effects that could harm the patient.

INTRODUCTION

Gout, the disease of kings, is an old lifestyle disease (Wortmann, 2008), was one of the earliest disorders to be recognized as a clinical entity. In ancient Egypt, gout was known among the Egyptians as Podagra (foot pain) as early as 2640 BC and was described by Hippocrates in the fifth century BC as the "unwalkable disease", mostly affecting the rich (Benedek and Rodnan, 1982; Nuki and Simkin, 2006). By the first century AD, a Roman senator named Seneca highlighted the role of genetics in gout. He noted that women becoming increasingly afflicted by gout, supposedly based on women's rivalry with men in living lavish lifestyles. Around the same time, Galen described 'tophi' as the manifestation of longstanding gout, and by the sixth century a physician named Alexander of Tralles discovered hermodactyl (a source of colchicines) while searching for a laxative. He was the first to use it to treat gout (Benedek, 2008). Recently, the prevalence of gout and the clinical profile of this disease become increasingly complex, due to large numbers of cases with iatrogenic factors, multiple comorbidities, advanced age, and hyperuricemia and arthritis refractory to treatment **(**Terkeltaub, 2010). Dietary causes of gout represent about 12% of total gout causes (Chen and Schumacher, 2008) including; a strong association with the consumption of alcohol, fructose-sweetened drinks, meat, and seafood **(**Terkeltaub, 2010; Weaver, 2010). Recent studies found dietary factors once believed associated are, in fact, not, including the intake of purine-rich vegetables (e.g., beans, peas, lentils, and spinach) and total protein **(**Choi *et al*, 2004; Weaver, 2010). The consumption of coffee, vitamin C and dairy products, as well as physical fitness, appear to decrease the risk (Hak and Choi, 2008; Williams, 2008; Choi, 2010). This is believed partly due to their effect in reducing insulin resistance **(**Choi, 2010).

Gout, a common metabolic disorder, is characterized by chronic hyperuricemia, which is defined as urate levels >6.8 mg/dl (≥360 µmol/L), which represent increasing in the physiological saturation threshold (Mandell, 2008). Gout manifests as microscopic and macroscopic soft tissue deposits of monosodium urate monohydrate crystals (tophi), which characteristic with excruciating pain, and articular and periarticular inflammation. Tophi can also promote chronic inflammatory and erosive arthritis (Chen and Schumacher, 2008). In some patients, gout also manifests as uric acid urolithiasis, promoted in part by urine acidity (Liebman, 2007). Allopurinol, the raw material of zyloric drug, is used primarily to treat hyperuricemia and its complications, including chronic gout.

The mechanism of action depending on that allopurinol is the structural isomer of hypoxanthine, a naturally occurring purine in the body and is an inhibitor of the enzyme xanthine oxidase. Xanthine oxidase is responsible for the successive oxidation of hypoxanthine and xanthine, resulting in the production of uric acid,

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the product of human purine metabolism (Pacher *et al*, 2006). In addition to blocking uric acid production, inhibition of xanthine oxidase causes an increase in hypoxanthine and xanthine. While xanthine cannot be converted to purine ribotides, hypoxanthine can be salvaged to the purine ribotides adenosine and guanosine monophosphates.

Increased levels of these ribotides may cause feedback inhibition of amidophosphoribosyl transferase, the first and rate-limiting enzyme of purine biosynthesis. Allopurinol, therefore, decreases uric acid formation and may also inhibit purine synthesis (Cameron *et al*, 1993). Scientists examined the composition of plasma and urine in patients with recurrent calcium calculi treated with allopurinol and found that plasma parathyroid hormone (PTH) was gradually increased in patients treated with allopurinol during treatment.

In patients treated with allopurinol and thiazide, plasma and urinary uric acid, plasma potassium and urinary calcium were decreased during treatment (Kohri, 1987). Intriguingly, we suggest that as human lifestyle changes, the severity of gout disorder will be altered and the challenge for the future will not only be how to control pain and lowering urate levels effectively, but also the associated implications in patients with gout including the effect of the gout drugs on human hormone profile which may cause multiple and complex dysfunctions within sex or/and thyroid functions for example which in turn imbalance the body homeostasis.

Overall, the previous observations encouraged us to investigate the impact of the anti-gout agent allopurinol on human hormone profiles including; 1) Sex hormones profile; Follicle-stimulating hormone (FSH), Estradiol (E2), Luteinizing hormone (LH), Prolactin, Progesterone, Dehydroepiandrosterone (DHEAS), and Testosterone, 2) Thyroid hormones profile; Thyroid-stimulating hormone (TSH), triiodothyronine (T3), and Thyroxine (T4), 3) Fasting Insulin, and Cortisol.

MATERIAL AND METHODS

Subjects

Eighty four adult volunteers with age range 16-21 years (n = 23) and 22-60 years (n = 12), and over 60 years (n = 7) were enrolled in the prospective study. Those individuals were divided into two main groups: 42 gouty patients and 42 healthy controls. Volunteers were sub-divided according to weight into three categories: 40-70 Kg (n =20), 70-100 Kg (n = 13), over 100 Kg (n = 9), and gender into 20 males and 22 females. The study protocol and informed consent were approved by the Ethics Committee of the National Research Centre.

Regarding to the present study, it was proved that the beginning of the fertile human volunteers or the adult group will begin from 16 years old to over 60 depending on the doctor prescriptions which based on the concentration of the drug intake, alternatively never affect. Patients received zyloric (allopurinol) treatment for duration period of 30-45 days.

Methods

Sera separated from whole blood samples which were withdrawn from males and females to measure serum Follicle-stimulating hormone (FSH), Estradiol (E2), Luteinizing hormone (LH), Prolactin, Progesterone, Dehydroepiandrosterone (DHEAS), Testosterone, Thyroid-stimulating hormone (TSH), triiodothyronine (T3), Thyroxine (T4), Fasting Insulin, and Cortisol collecting at A.M. and P.M. All hormone concentrations were determined quantitatively using ELISA Kits provided by DRG International, Inc., USA, Diagnostic Systems Laboratories. Inc., and Adaltis Italia SPA Company, Italy.

Statistical Analyses

Data were statistically described in terms of range, mean, standard deviations (± S.D.), and frequencies (number of cases) when appropriate. Comparison of variables between the study groups had been done using analysis of variance (ANOVA) test. A probability value (P-value) less than 0.05 was considered statistically significant. Statistical calculations had been done using statistical computer program: SPSS (Statistical Package for the Social Science; SPSS Inc., version 17.0, USA).

RESULTS

Follow up data were available for all patient volunteers who have gout or gouty arthritis and had been treated with zyloric (allopurinol) drug. The clinical features of all individuals were summarized in Table 1. Table 1 illustrates that adult patients of ages ranged from 16 years old to over 60 years who were received zyloric (allopurinol) drug, for duration period extended from 30-45 days. Beans, meat, tea and peas represent the main dietary causes of gout in Egypt (43%, 28%, 17%, 9%; respectively). As is clear from these percentages, beans represent the highest percentage of dietary causes of gout.

Therefore, we recommend nominating the disease of kings or gout disorder in Egypt with a new name "EA Disease" ascribed to the "E" and "A" alphabetic characters included within the major sources of gout among Egyptian patients "m***ea***t, b***ea***ns, t***ea***, and p***ea***s" (Fig. 1). Male and female patients who received zyloric (allopurinol) drug have high significant alteration ($P<0.05$) in all serum hormones except Luteinizing hormone (LH) in males have non significant difference as compared to the control group. Patients who received zyloric (allopurinol) have significant increase ($P<0.05$) in serum Follicle-stimulating hormone (FSH), Estradiol (E2), Luteinizing hormone (LH), Prolactin, Progesterone, Testosterone in femles, Thyroid-stimulating hormone (TSH), triiodothyronine (T3), Thyroxine (T4), Fasting Insulin, and Cortisol collecting at P.M. in males as compared to the control group. Furthermore, Patients who received zyloric (allopurinol) have significant decrease ($P<0.05$) in serum Dehydroepiandrosterone (DHEAS), Testosterone in males, Cortisol collecting at A.M., and P.M. in females as compared to the control group.

Table. 1: Hormone levels of patients and healthy controls.

Hormones Mean ± SD	Controls				Patients					
	Male		Female		Male			Female		
	M	SD	M	SD	M	SD	P	M	SD	P
FSH (mIU/ml)	5.1	0.1	9.0	0.1	6.0	0.1	**S***	14	0.1	**S***
E2 (pg/ml)	12.3	0.6	33.2	0.2	28	0.1	**S***	36	0.2	**S***
LH (mIU/ml)	1.5	0.8	4.5	1.5	1.7	0.1	NS	2.2	1.1	**S***
Prolactin (ng/ml)	5.7	0.3	12.0	0.3	9.0	0.2	**S***	13.0	1.2	**S***
Progesterone (ng/ml)	0.2	0.4	0.7	0.2	1.6	0.2	**S***	1.9	1.4	**S***
TSH (µIU/ml)	0.4	0.1	0.4	0.2	2.3	0.2	**S***	2.9	1.2	**S***
T3 (ng/ml)	1.4	1.1	1.4	0.3	3.7	0.2	**S***	3.2	1.1	**S***
T4 (ng/dl)	0.5	0.2	0.8	0.3	2.1	1.1	**S***	1.8	0.7	**S***
DHEAS (µg/dl)	156.0	1.4	198	1.7	37	1.3	**S***	106	0.9	**S***
Fasting Insulin (mIU/ml)	16.0	1.1	16.4	0.5	19.0	1.9	**S***	19.0	0.6	**S***
Testosterone (ng/dl)	1.0	0.1	0.8	0.1	0.14	0.7	**S***	1.4	0.5	**S**
Cortisol at a.m. (mg/dl)	27.4	0.1	27.4	0.2	7.6	0.9	**S***	3.3	0.5	**S***
Cortisol at p.m. (mg/dl)	1.4	0.2	8.4	1.1	3.3	0.5	**S***	5.5	0.1	**S**

All data were represented in term of mean (M) and standard deviation (SD).Drug; Zyloric P= P-value, S*; represents high significant difference (P<0.001), S; represents significant difference (P<0.05), NS; represents non-significant difference (P>0.05).

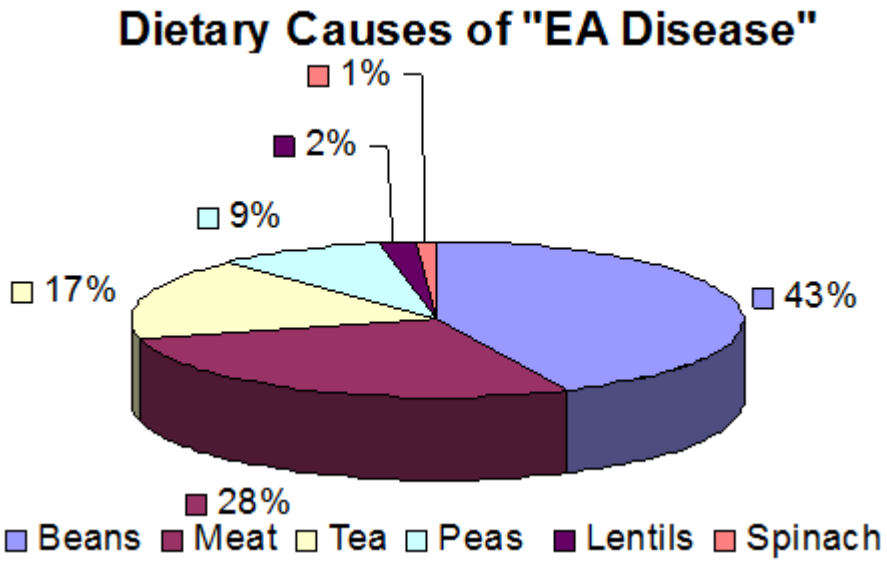

Fig. 1: Dietary causes of gout or EA disease in Egypt.

DISCUSSION

This study has been established to investigate the impact of zyloric (allopurinol) drug on human hormone profiles among patients suffering Podagra (foot pain). Recently, authors have designed a new study to evaluate the effect of some digestive-relevant drugs on different hormone profiles for providing new medical guidelines to alter the drug dose according to the effect of the drug on the different human hormone profiles and it is extremely important to avoid a lot of burden and negative side effects that could harm the patient health **(**Eskander *et al*, 2013). This previous study encouraged us to establish the current study for providing the effect of zyloric on human hormones among patients suffering from gout.

The new nomenclature, EA disease or gout, as mentioned in the current study is ascribed to the "E" and "A" alphabetic characters included within the major sources of gout among Egyptian patients "m***ea***t, b***ea***ns, t***ea***, and p***ea***s". These results are agreed with the previous data suggested that dietary causes of gout include; a strong association with the consumption of alcohol, fructose-sweetened drinks, meat, and seafood **(**Terkeltaub, 2010; Weaver, 2010). Furthermore, recent studies have found dietary factors once believed associated are, in fact, not, including the intake of purine-rich vegetables (e.g., beans, peas, lentils, and spinach) and total protein **(**Choi *et al*, 2004; Weaver, 2010). Additionally, authors introduced coffee, vitamin C as anti-gout dietary products appear to decrease the risk of this disease (Hak and Choi, 2008; Williams, 2008; Choi, 2010).

Intriguingly, both males and females receiving zyloric (allopurinol) drug have high significant alteration in all serum hormones except LH in males have non significant difference as compared to the control group. Furthermore, volunteers receiving zyloric (allopurinol) have significant increase in serum FSH, E2, LH, Prolactin, Progesterone, Testosterone in femles, TSH, T3, T4, Fasting Insulin, and Cortisol collecting at P.M. in males as compared to the control group. Our results agreed with authors who suggested that allopurinol affects thyroid hormones among gouty patients and found that plasma parathyroid hormone (PTH) gradually increased in patients treated with allopurinol during treatment (Kohri, 1987). On the other hand, the present study

found that individuals receiving zyloric (allopurinol) have significant decrease in serum DHEAS, Testosterone in males, Cortisol collecting at A.M., and P.M. in females as compared to the control group.

It was suggested that allopurinol is not only has been used for the treatment of gout and conditions associated with hyperuricemia, but also it has a potential effect on cancer treatment. Allopurinol did not expose cytotoxicity as a single treatment in human hormone refractory prostate cancer cell lines, PC-3 and DU145.

However, allopurinol drastically induced apoptosis of PC-3 and DU145 in combination with tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), which is a promising candidate for anticancer agent but its efficacy is limited by the existence of resistant cancer cells. Authors examined the underlying mechanism by which allopurinol overcomes the resistance of prostate cancer cells to TRAIL. Therefore, they show the novel potential of allopurinol in cancer treatment and indicate that the combination of allopurinol with TRAIL is effective strategy to expand the TRAIL-mediated cancer therapy (Yasuda *et al*, 2008).

Amazingly, the human lifestyle changes mainly dietary lifestyle is associated with the persistence and severity of gout disorder. Therefore, we have to optimize and standardize the dietary intake which does not lead to disorders or its implications. Moreover, the changes of the lifestyle will alter the challenge for the future.

On the other hand, these alterations within male and female sex hormones profile within the present study may lead to malfunction within the physiological performance of both males and females in addition to negative psychological effects, therefore the determination of drug dose must be dependent on its effect on human hormones profile.

In conclusion, the zyloric (allopurinol) alter the human sex and thyroid hormones profile among patients suffering Podagra (foot pain) and the present study may be useful in drug dose optimization depending on the effect of the drug on each human hormone, in the addition of new medical guidelines for drug companies and to avoid negative side effects that could harm the patient.

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