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SOME BIOCHEMICAL CHANGES AFTER TREATMENT IN IRAQIS ACROMEGALIC PATIENTS

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ABSTRACT
Acromegaly is a rare disease produce generalize and serious alteration in the patient with active disease. Many of these patients are also diabetic. Many analytes, hormones, markers are change in these disease. The objective of study is to assess the modification in a number of parameters that changed during the acromegaly as a result of excess in GH and IGF-1 levels. The study included 36 patients and 38 healthy controls, paired by sex and age and BMI. Serum concentration of GH and the other parameters including (insulin, glucose, lipid profile, uric acid) were determined by biochemical method .Compared to controls, acromegalic patients had increased levels of GH, insulin, glucose, triglyceride, very low density lipoprotein(VLDL) ($p<0.05$) , High density lipoprotein (HDL) significantly reduce among acromegalic patients compared to the control group ($p<0.05$) . Non significant differences in total cholesterol, low density lipoprotein (LDL) levels between controls and patients group ($p>.0.05$).

KEYWORDS: Acromegaly patients, diabetic, cholesterol, LDL, VLDL, GH etc.

INTRODUCTION

Acromegaly is an uncommon disorder characterized by excess secretion of growth hormone (GH)[(1)], causes excessive growth of tissues over a period of many years. Most noticeable changes in untreated patient are enlargement of the hands, the feet, the brow and nose are enlarged, the zygomatic arches and jaw are prominent and the abundant facial tissue contains deep nasolabial folds. These changes take place so slowly that they are not recognized, especially by persons who see the patient frequently [(2)]. Acromegaly is a rare disease, with a prevalence of 40 to 70cases per million inhabitants and an annual incidence of 3 to 4 new cases per million [(3)]. Untreated acromegalic patients associated with many complications, Cardiac involvement is common in acromegaly. Evidence for cardiac hypertrophy, dilation and diastolic filling abnormalities has been widely reported in literature [(4)]. Skin change [(5)]. Increase bone mineral [(6)], Body mass index changes [(6,7)], Respiratory complications [(3)]. Rheumatological complication[(8)], neuropathies [(9)] are common in acromegalic patients.

Patients with acromegaly have an increased prevalence of hypertension and disturbances of intermediary metabolism, including insulin resistance and increased metabolic rate. Increased levels of triglycerides have been reported in acromegaly, whereas hypercholesterolemia has been inconsistently found [(10)].

The prevalence of diabetes mellitus and that of impair glucose tolerance in acromegaly is reported to range 16–56%, whereas the degree of glucose tolerance seems correlated with circulating growth hormone (GH) levels, age, and disease duration[(11)]. Excess amounts of GH and IGF1 interacts with metabolic regulation, and indeed, GH hyper secretion is associated with hepatic and peripheral insulin resistance this and also other mechanisms lead to the development of diabetes mellitus [(12)] . The effect of GH on glucose metabolism is complex. It has an acute insulin-like effect and a chronic insulin-antagonistic and diabetogenic action. The insulin resistance occurs primarily in muscles and is due to a post receptor defect and decreases glucose up take. At the post receptor level, GH decreases auto phosphorylation of the insulin receptor and glucose transporters. An increase in the hepatic glucose output has also been implicated as a cause of hyperglycemia in acromegaly[(13)]. Basal metabolic rate (expressed per kg body weight) is increased in acromegaly [(14,15)]. GH and IGF-1 excess is associated with alterations in body composition, including an increase in body water and lean body mass, and a reduction in body fat[(16)]. Hypertriglyceridemia occur in 19 to 44 % of acromegalic patients. There is positive correlation between serum insulin response to glucose and increased serum triglyceride concentration. Hepatic triglyceride lipase and lipoprotein lipase activity are decrease in acromegaly and may contributed to the hypertriglyceridemia in those patients [(17)] .The aim of the present study to assess the number of analytes including (insulin, growth hormone, glucose, lipid profile, uric acid) among Iraqis' acromegalic patients living in Baghdad.

MATERIALS AND METHODS

Subjects

36 patients with active acromegaly were examined in the national diabetic's center

In Baghdad. Patients had diagnosis of active acromegaly that comprised clinical examination and an increase in the serum levels of GH and/or IGF-1[(18)] .Most of them have history of the disease at least more than one year and all they received octreotide therapy regularly every month in that center. The control group was 38 healthy men,

matched by sex, age and BMI with the acromegalic patients.

Sample

Blood samples were obtained from the antecubital vein between 8 AM and 9 AM and after a 12-hour fast. Samples were centrifuged at 2000 rpm for 15 minutes thenthe serum aliquots were obtained used to determine the levels of glucose, lipid profile and uric acid.

Analytic Determinations

Standardized methods with quality control procedures were used to determine the plasma level of these analytes. Serum concentration of all of analytes (glucose, lipid profile, uric acid) were measured using biochemical methods [18-23] .

Statistical analysis

Mann-Whitney Test use to examine the significance of differences between control group and acromegalic group .Data were expressed as mean ± standard deviation (SD) and Mann-Whitney Test was used to compare means. That test was performed using the statistical package for social science (SPSS 14).

RESULTS

Demographic presentation of 36 acromegalic patients and 38 controls were elucidated in table (1). Table (2) shows the glucose levels, insulin levels, insulin resistance and β cell function of the 36 acromegalic patients and of the38 healthy controls, age, weight and BMI express as mean ± standard deviation of the mean. Table (3) shows the lipid profile levels of the 36 acromegalic patients and of the38 healthy controls express as mean ± standard deviation of the mean.

TABLE 1: shows the growth hormone and uric acid levels of the 36 acromegalic patients and of the38 healthy controls express as mean ± standard deviation of the mean.

Character	Total Acromegalic N=36 (%)	Control N=38(%)
Average age	48.06± 11.47	50.06± 12.47
Average weight	90.03± 19.33	84.32± 16.98
Average body mass index (BMI)	33.17± 5.62	30.67± 4.9
Smocking	4(11.11%)	5(13.15%)
Alcoholism	1(2.77%)	0(0.00%)
Diabetics	16(44.44%)	1(2.63%)
Hypertension	16(44.44%)	6(16.66%)
Heart disease	5(13.88%)	1(2.63%)
Osteoarithritis	4(11.11%)	2(5.26%)
Hyperthyroidism	2(5.55%)	0(0.00%)
Hypothyroidism	2(5.55%)	0(0.00%)
Renal disease	1(2.77%)	1(2.63%)
Gastric problem	1(2.77%)	0(0.00%)
Asthma	1(2.77%)	0(0.00%)
Sandostatin use	36(100%)	0(0.00%)
Family history of diabetes	14(38.88%)	12(31.57%)
Family history of hyper tension	11(30.55%)	18(47.36%)
Family history of premature death (<45)	4(11.11%)	0(0.00%)

TABLE 2. Serum Glucose level, serum insulin level, HOMA index among control group and acromegalic group

Groups parameters	control group (n=38)	acromegalic group (n=36)	Degree of significance
Fasting serum glucose (mg /dL)	110.84± 14.90	176.22 ± 77.50*	P = 0.00
Fasting serum insulin (μIU/ml)	9.99± 9.42	18.26 ± 14.79*	P = 0.013
HOMA -IR	2.84 ± 2.87	9.05 ± 9.35*	P = 0.00
HOMA-β%	73.67±60.36 %	67.84 ±66.99 %	P = 0.053

Value were presented as mean ± standard deviation of mean; n=number of subject, (*) = significance difference, (P<0.05) with respect to control group and acromegalic group.

HOMA = homeostatic model assessment, % B = estimates steady state beta cell function, IR = insulin resistance.

TABLE 3: LDL, cholesterol, HDL, VLDL, triglyceride level among controls group and acromegalic patients group

Groups parameters	controls group (n=38)	Acromegalic group (n=36)	Degree of significance
Serum cholesterol (mg /dL)	187.28 ± 55.05	200.44 ± 67.66	P = 0.604
Serum LDL (mg /dL)	108.52 ± 57.38	128.27 ± 64.24	P = 0.161
Serum HDL (mg / dL)	53±39.94	44.44± 13.88*	P = 0.048
Serum VLDL (mg / dL)	20.81±5.87	55.16 ±40.11*	P = 0.00
Triglyceride (mg / dL)	103.55±32.22	165.52±120.41*	P = 0.01

Values were presented as mean ± standard deviation of mean; n=number of subjects, (*) = significance difference, (P<0.05) with respect to controls group and acromegalic patients.

TABLE 4: Growth hormone, uric acid levels among controls group andacromegalic group

Groups Parameters	Controls group (n=38)	Acromegalic patients group (n=36)	Degree of significance
Growth hormone (ng/ml)	1.88± 2.48	9.70± 9.83*	P = 0.00
Uric acid (mg / dL)	4.36± 1.43	5.13± 1.63*	P = 0.041

Values were presented as mean ± standard deviation of mean; n=number of subjects, (*) = significance difference, (P<0.05) with respect to controls group and acromegalic patients.

DISCUSSION

The table (4) showed GH levels among acromegalic patients significantly higher than those in control group, irregularity in dose taken is the most important reason contributed to these differences. The present study showed serum glucose levels among acromegalic patients significantly higher than those in control group. This result is in agreement with what found by Piniewska-Hułas and his co-workers (1996) [24]. Coronary risk factors like hypertension, insulin resistance, diabetes mellitus, and dyslipidemia are frequent complications of acromegaly [25]. As it is mentioned before, GH has initial effect of increasing insulin levels. However, the predominant effect of prolong GH excess is to increase blood glucose levels despite an insulin increase. Although the precise mechanisms remain poorly understood, the insulin receptor of acromegaly is characterized by defects in the ability of insulin both to suppress hepatic glucose production and by impairment of glucose oxidation and uptake into peripheral tissues. Decrease in glucose uptake is likely to be important in the pathogenesis of impair glucose tolerance in acromegaly [26]. Rizza R.A. and co-workers (1982) [27] concluded that the increases in plasma growth hormone can cause insulin resistance in man, which is due to decreases in both hepatic and extra hepatic effects of insulin and this decrease in insulin action can be explained on the basis of a post receptor defect. The effect of free fatty acid (FFA) on the partitioning of intra-cellular glucose fluxes was originally described by Randle et al. [28].According to his hypothesis (the glucose/fatty acid cycle), oxidation of FFA initiates an up-stream, chain-reaction-like inhibition of glycolytic enzymes since FFA is important alternative sources of acetyl coA, which ultimately inhibits glucose uptake and this theory agree with present study.

The present study showed serum insulin levels among acromegalic patients significantly higher than those in controls group. Several studies agreed with this finding [24,29]. Many people's with acromegaly develop insulin resistance and type 2 diabetes. The mechanisms for the development of diabetes mellitus in acromegaly is that excess of the growth hormone, which itself counteracts the action of insulin. So, elevated growth hormone levels causes excess hepatic glucose production and defective utilization at peripheral cause stimulate insulin release [30].

The present study showed increased cholesterol levels among acromegalic patients. But fail to rise significantly higher than those in controls group. This result agreed with M. Arosio and his co-workers (1999) [31].Although growth hormone have important role on lipid metabolism and showed no differences on total cholesterol. However, they exert different effects on different lipid profile components (LDL, HDL, etc….). In the present study, non -significant change in total cholesterol levels could be assumed as a result of GH affect on both pathways that interfere with total cholesterol levels (cholesterol synthesis and cholesterol metabolism) in the same extent and gave net difference approximate to zero as a result of these multiple action of GH . M. Rudling and his co-workers (1997) [32] act on hypophysectomized rats to determine the effect of growth hormone deficiency and appeared that the activities of the rate-limiting enzymes in cholesterol and bile acid biosynthesis, 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG CoA reductase) and cholesterol 7alpha-hydroxylase (C7alphaOH), were reduced by 71% and 64%, respectively. (HMG CoA reductase) important for cholesterol synthesis and (C7alphaOH) important for cholesterol metabolism. Also, LDL receptor expression was reduced by 18% in rat and there by alter LDL and so cholesterol metabolism.

The present study showed LDL levels among acromegalic patients were non- significantly higher than those in control group. Despite increase in the mean of LDL among acromegalic patient, this increment is not highly enough to become statistically significant. Dyslipidemia one of the frequent complications in acromegaly. Several studies showed that most of the patients with uncontrolled acromegaly and those were newly diagnosed having high level of growth hormone showed worsen dyslipidemia and significant elevation of LDL levels [33,34]. However, M. Arosio and his co-workers (1999) [31] showed that the LDL levels significantly decrease in patients received growth hormone antagonist therapy specially Octreotide and there was highly link between growth hormone and LDL levels, and reduction in growth hormone cause normalize of LDL levels in acromegalic patients and this agree with present study since all of the patients in this study were on octreotide therapy.

The present study showed HDL levels among acromegalic patients significantly lower than those in control group. This result agreed with work of M. Arosio and his co-workers (1999) [31] and agreed with Colao and his co-workers (2001) [35]. Few studies tried to explain the effect of growth hormone on HDL levels in acromegalic patients. One of these studies showed that reduction of HDL in acromegaly could be attributed to the reduction in enzymes that plays a key role in regulation of HDL cycle within the body. the study showed the activity of Lecithin cholesterol acyl transferase (LCAT), Cholesteryl ester transfer protein (CETP), phospholipid transfer protein (PLTP) significantly reduce among the acromegalic patients in compare to control group. Lecithin cholesterol acyl transferase (LCAT) has the ability to esterifies free cholesterol (FC) in HDL is one of the important step in reverse cholesterol transfer to the liver .Cholesteryl ester transfer protein (CETP) is able to transfer Cholesteryl esters from HDL to very low and low density lipoproteins

(VLDL and LDL). While phospholipid transfer protein (PLTP) plays important role in the interaction of HDL with cholesterol and phospholipid molecules from cells and other lipoproteins so disturbance in these enzyme affect on HDL cycle[36]. Apo lipoprotein A1 (apoA1) levels reduce in acromegalic patients in several studies and this might be play crucial role in reduce HDL levels since apoA1 protein abundant in HDL and their reduction may result from reducing its synthesis by the liver as a result of excess growth hormone levels in acromegalic patients . This is in agreement with Parkinson C and his co-workers (2002) [37].Study by J. Pietzsch and his co-workers (1998) [38] suggested that increased apolipoprotein A-I catabolism in subjects with impaired glucose tolerance in respect to controls group. Since 16(44.44%) of the patients in present study were documented as a diabetics and received diabetes therapy and many of non diabetics patients in present study have impaired glucose tolerance, so it can be considered the J. Pietzsch study as another way to explain reduction in HDL levels among acromegalic patients from point of apoA1 levels and impair glucose tolerance.

The present study showed VLDL levels among acromegalic patients significantly higher than those in control group. Vilar L. and his co-workers (2007) [39] agreed with this study. Elevation of VLDL levels could be explained by various ways depending on several studies. One of the important effects of growth hormone on VLDL levels is direct increase production and secretion of apo B protein which is one of principle protein in VLDL composition. DANIEL LINDE´ N. and his co-workers (2000)[40]gave like results. Study by L. Boero and his co-worker (2000)[41] showed significance increase in (CETP) protein levels which can be consider as a possible way to increase in VLDL levels by acromegalic patients . Another reason in this study which works on impair glucose tolerance patients is that suppression of plasma lipoprotein lipase activity that need insulin for optimal activity resulting accumulation of VLDL in the serum.

The present study showed serum triglyceride levels among acromegalic patients significantly higher than those in control group. Several studies agree with this finding [42,43] . Higher triglyceride levels attributed to many reasons: first of all, although all of the patients in present study received octreotide therapy, the growth hormone levels are very significantly higher from the controls group. So, even the patients received therapy, they still as active acromegalic patients. Other important factor is that, 28(73 %) of acromegalic patient in this study having impair glucose tolerance and 16(44.44%) are diabetics, and according to the table (2) the HOMA- IR in the patients group are high and significantly different from the controls group. So, most of the patients had insulin resistance. Insulin resistances means reduce insulin action that cause enhance lipolysis since the insulin is potent inhibitor of lipolysis. This causes elevated non estrifeied free fatty acid (NEFFA) levels. In the liver NEFFA are converted to acetyl CoA and ketones or reesteirfied to form endogenous triglyceride and incorporate to VLDL and so increase triglyceride levels[2]. Study by Nikkilä EA and his co-worker (1975) [44] showed that the patients with highest plasma-insulin response had significantly higher serum triglyceride than the rest of the acromegalic group and increased serum triglyceride was associated with increased production rate. The effect of growth hormone on triglyceride levels could be explained in different models. One of them is that growth hormone effect on insulin resistance that modified triglyceride levels as described above .While other model explained by study of Ryoyu Takeda and his coworker (1982) [45] that showed reduction in hepatic triglyceride lipase activity caused by direct effect of high level of GH and thereby reduce in metabolism of triglyceride and so elevation in its level .

The present study showed uric acid levels among acromegalic patients significantly higher than those in control group. Naznin Dixit and his co-worker (1996) [46]showed uric acid levels elevated following growth hormone therapy , in other mean direct relationship between GH and UA and this comparable to present study . Because 70% of the urate are excreted through the kidney, so the kidney is the major source for UA elimination and any factor affect the kidneys function could interfere with UA levels [47]. Growth hormone (GH) has antidiuretic and antinatriuretic effects in rats and humans. But the molecular mechanisms responsible for these effects are unknown [48]. A number of studies determined the GH risk in Urolithiasis and stone formation which may develop to further disease as a renal failure that may contributed to reduce uric acid excretion [49]. Also, many studies showed high incidence of renal failure among acromegalic patients [50]. Very few studies determined the direct effect of GH on UA excretion as in study by Renata S. Auriemma and his co-workers (2010) [51]which showed variation in the urinary excretion of uric acid in which lowest excretion showed in active acromegalic group (uncontrolled acromegaly with high GH levels) followed by control acromegalic group (acromegalic patients received therapy with normal GH levels) then control group that showed high urinary UA excretion , further research necessary in this field .

In conclusions, there were alteration in a number of analytes in acromegalic patients , the hyperglycemia and alteration in triglyceride and VLDL are predominant, while other lipid profile parameters are less effected by elevation of GH levels , uric acid are less correlated with GH .

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