Some Hormonal and Biochemical Disorders in Patients of Down's syndrome in Egypt

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ABSTRACT

Background: *Down syndrome (DS) is caused by an extra chromosome 21 and is the most common autosomal chromosome aberration. Down syndrome results in mental retardation and several congenital malformations.* ***The aim:*** *The purpose of this study is to shed light on the importance of follow-up screening analysis of some hormones and some biochemical parameters in patients with Down syndrome.* ***Methods:*** *Laboratory variables in 31 adult patients with Down's syndrome were compared with those of 30 matched controls. Fasting blood samples were collected for estimation of free thyroxin (FT_4), thyroid stimulating hormones (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E_2), free testosterone (T), as well as serum levels of creatinine, uric acid and albumin.* ***Results:*** *The thyroid function tests documented a higher mean TSH and lower FT_4 mean levels in Down's syndrome than in controls. FSH and LH mean levels were significantly higher in DS group than in controls ($p<0.05$). The mean level of estradiol (E2) in females with DS (11.61±2.28 pg/ml) was significantly lower than controls (31.18±2.71 pg/ml) ($p<0.05$), while the level of free testosterone (fT) was significantly higher compared with control subjects (2.71±0.66 pg/ml versus 1.2±0.37 pg/ml respectively, $p<0.05$. As well as, in males DS patients, the level of E_2 was normal (11.33±1.04 pg/ml) while the level of free testosterone was significantly lower compared with controls (1.98±0.21 pg/ml) and (2.63± 0.44 pg/ml) respectively. Also, levels of serum creatinine and uric acid in DS patients were higher compared with controls, while the level of albumin was low ($p<0.05$).* ***Conclusion:*** *Through the results of measuring some hormones and biochemical changes in this study of Down syndrome patients compared to healthy subjects, it turns out DS patients are more vulnerable to diseases than others, such as renal and hepatic diseases, infertility and should be followed to keep under control.*

Key words: *Down syndrome. fT_4, FSH, E_2, LH, free testosterone, Albumin, Kidney function.*

INTRODUCTION

Down syndrome, or Trisomy 21, is the most common serious autosomal chromosome aberration in which affected individuals survive beyond infancy[(1)]. Investigations suggest an increased incidence of gonadal dysfunction in patients with Down syndrome. New features, Alzheimer disease and osteoporosis emerge in these individuals. Therefore, hormonal investigation in persons with Down syndrome is pursued[(2)]. Thyroid disease is common in Down syndrome with both congenital hypothyroidism and

autoimmune thyroid disease occurring more frequently than in the general population. Patients with DS are also more likely to have elevated Thyroid Stimulating Hormone (TSH) [3]. Both exert a negative effect on TSH bioactivity, only compensated by the very high levels of the hormone as in adult Down syndrome [4]. In adult DS, the mean serum levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were significantly elevated above the mean for normal men[5].

Hypothyroidism is associated with many biochemical abnormalities including increased serum creatinine and uric acid levels. The serum creatinine concentration increases in hypothyroid patients due to reduction of glomerular filtration rate because of hemodynamic changes in severe hypothyroidism as in Down syndrome[6]. Also, Down syndrome is associated with a low serum albumin concentration, independently of the presence of liver disease. The advent of Alzheimer's Disease in may be associated with a rise, in serum albumin concentrations [7].

The purpose of the present study is to shed light on the importance of follow-up screening analyzes of some hormones and some biochemical changes in patients with Down syndrome.

PATIENTS & METHODS

Adult individuals with Down syndrome were recruited from the Genetics Unit, Children Hospital, Mansoura University. All the patients in the study were diagnosed by karyotyping. Thirty one patients suffering from DS (trisomy 21), 13 females and 18 males, the age ranged 14–32, with a mean age of 21.25±4.94 years and thirty individuals age and sex matched, 14 females and 16 males, their ages ranged from 13 - 35, with a mean age of 22.13±5.80 years as controls were included in the study. Informed consent was obtained from patients' parents and controls. The study was approved by the Mansoura University Ethics Committee.

Serum was isolated from blood samples collected after an overnight fast. Serum TSH was determined by MICRO-ELISA Test Kit USA[8], serum fT_4 was measured by enzyme immunoassay kit for the quantitative determination of Free T4 concentration in serum, USA [9], serum LH was determine according to **Knobil**,[10] also, serum FSH was measured according to **Mehta**, [11], serum Estradiol by **Arakawa *et al.*,** [12] and serum free Testosterone measured by the method of **Trachtenberg** [13]. Serum uric acid and creatinine were determined by an enzymatic method using biomerieux/France kit [14] and colorimeter method using (Syrbio/ France) kit [15] respectively. Recombinant serum albumin, produced in yeast and supplied by Delta Biotechnology Ltd. (Nottingham, UK), was purified by gel filtration, complexed with excess myristic acid, and crystallized as described previously [16].

Statistical Analysis:

The software SPSS 17 was used for the statistical analysis, with the results expressed as mean ± standard deviation (Mean ± SD). The distribution of the group was determined by means of the

Kolmogorov-Smirnov test, showing a normal distribution for both groups. The Student unpaired "*t"* test and the ANOVA test were used for the group comparisons. Significant differences were considered with a *P*<2*0.05.

RESULTS

Table 1 and figure 1 showed the comparison between levels of serum fT_4, TSH, FSH, LH, E_2 and fT in DS patients with control subjects.

Table 1: Serum levels of fT_4, TSH, FSH, LH, E_2 and fT in Down syndrome patients with control subjects (Mean ± SD**).**

Parameters	**Control subjects (n=30)**	**Down syndrome patienta (n=31)**
fT_4 (pmol/L) p	15.74±2.62	10.59±2.99 <0.05
TSH (mIU/L) p	1.81±0.50	6.69±0.98 <0.05
FSH (mIU/ml) p	9.13±2.21	25.81±2.96 <0.05
LH (mIU/ml) p	7.40±2.17	21.32±1.98 <0.05
E_2(pg/ml) p	22.49±9.07	11.23±.930 <0.05
fT(pg/ml) p	2.42±1.33	2.29±.58 =0.225

fT4, free thyroxin; TSH, thyroid stimulating hormones; FSH, follicle-stimulating hormone; LH, luteinizing hormone; E_2, estradiol; fT, free testosterone.

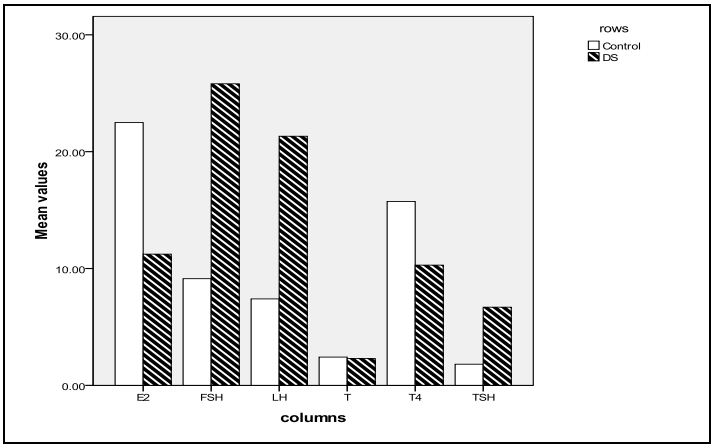

Fig 1: Mean serum levels of TSH, fT4,FSH, LH, fT and E_2 of DS patients and control subjects.

The thyroid function tests showed that mean TSH, FSH and LH levels were significantly higher, while fT_4 level was significantly lower in DS group than in controls (p<0.05 for each). The level of E_2 in females with DS was significantly lower than in controls (11.61±2.28 pg/ml versus 31.18±2.71 pg/ml respectively, (p<0.05), while the level of fT was

significantly higher compared with control subjects (2.71±0.66 pg/ml versus 1.2±0.37 pg/ml) respectively, p<0.05. On the other hand, male patients of DS, showed no significant difference in the level of E2 (11.33±1.04 pg/ml), while the level of testosterone (1.98±0.21 pg/ml) was significantly lower (P<0.05) compared with controls (1.98±0.21 pg/ml) and (2.63±0.44 pg/ml) respectively (table 2)

Table 2: Comparison between mean serum levels of E_2 and fT in females and males Down syndrome patients with control subjects (Mean ± SD**).**

Parameters	**Control females (n=14)**	**DS females (n=13)**	**Control males (n=16)**	**DS males (n=18)**
E_2 (pg/ml) p	31.18±2.71	11.61±2.28 <0.05	11.15±0.34	11.33±1.04 =0.468
fT (pg/ml) p	2.71±0.66	1.2±0.37 <0.05	2.63±0.44	1.98±0.21 <0.05

E2, estradiol; fT, free testosterone.

Table 3 and figure 2 showed the comparison between mean levels of serum creatinine, uric acid and albumin in Down syndrome patients with control subjects.

Table3: Comparison between creatinine, uric acid and albumin mean serum levels in DS patients with control subjects (Mean ± SD**).**

Parameters	**Control (n=30)**	**DS (n=31)**
Creatinine (mg/dl) P	0.82±0.16	1.62±0.28 <0.05
Uric acid (mg/dl) P	3.14±0.63	5.99±0.81 <0.05
Albumin (g./L) P	42.64±2.46	25.5±2.77 <0.05

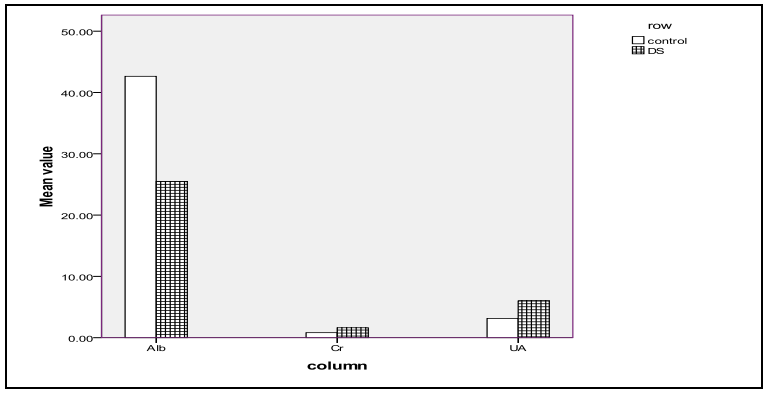

Fig 2: Mean serum levels of creatinine (Cr), uric acid (UA) and albumin (Alb) of DS patients and control subjects

The mean serum levels of creatinine and uric acid were significantly higher, while that of serum albumin was significantly lower in DS patients compared with to their corresponding mean levels in control subjects ($p<0.05$ for each). The uric acid (UA) levels were significantly higher in males with DS (6.59±0.43 mg/dl) than in the females DS (5.16±0.36mg/dl), *(P*<0.05) (table 4),(fig.3).

Table 4: Comparison between females and males' mean serum levels of uric acid and creatinine (Mean ± SD).**).**

Parameters	**females (n=13)**	**males (n=18)**
Uric acid (mg/dl)	5.16±0.36	6.59±0.43
p		<0.05
Creatinine (mg/dl)	1.37±0.19	1,80±0.19
p		<0.05

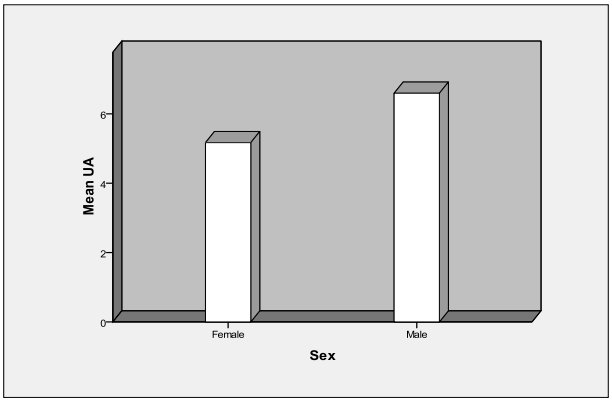

Fig. 3: Uric acid levels in serum males and females of Down syndrome patients.

Also, we found creatinine levels were significantly higher in males with DS (1.80±0.19 mg/dl) than in the females DS (1.37±0.19 mg/dl), *(P*<0.05) (table 4), (fig.4).

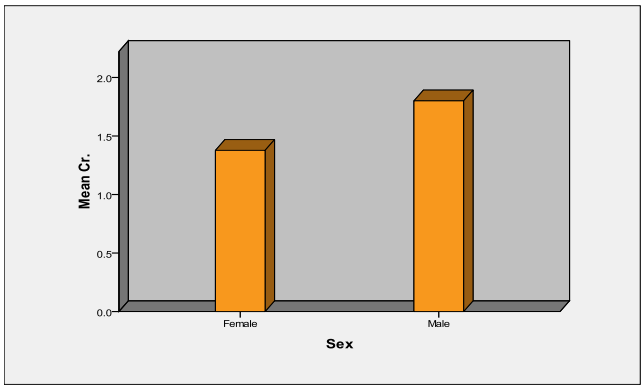

Fig. 4: Creatinine levels in serum males and females of Down syndrome patients.

DISCUSSION

Down syndrome was reported to be associated with premature ageing in all cells[(17)]. The clinical features of Down syndrome may be due to triplication of specific segments of chromosome 21[(18)], or the syndrome is the result of non-specific effects of aneuploidy interfering with gene replication[(19)]. The data indicate that thyroid dysfunction, in particular hypothyroidism, is common in adults with Down's syndrome, though specific tests are usually required to make the diagnosis. The general reduction in thyroid function in Down's syndrome may be due to impaired development of the thyroid gland. However, frank chemical hypothyroidism may occur only when thyroiditis is superimposed on preexisting diminished thyroid reserve[(20)]. Our results are consistent with those of **Shanlee Marie Davis** et al.[(3)], who found that, thyroid disease is common in Down syndrome with both congenital hypothyroidism and autoimmune thyroid disease occurring more frequently than in the general population. Patients with DS are also more likely to have elevated TSH.

Ying-Hui et al. [(21)] found that, in 23 men with DS, the mean serum levels of FSH and LH were significantly elevated above the mean for normal men, and the mean plasma level of T was normal, suggesting a diagnosis of partial gonadal deficiency, also, they found among 14 women in their study, 6 had primary gonadal dysfunction. This finding agrees with our results of FSH and LH but differ from the level of T, we found that, level of fT in males of DS was lower than controls, and that finding indicates that DS patients may be infertile.

Our finding of mean serum albumin level is lower in DS patients than in controls is comparable to those of other studies[(22,23)]. This finding may indicate that, these DS patients may have liver diseases.

Uric acid was found significantly elevated in primary hypothyroidism [(6)]. Our results confirmed the increased serum uric acid levels

reported for subjected with Down syndrome and also, the finding that it was more evident in men than in women reported by **Nagyova ei al.**[(24)]. Uric acid is associated with cardiovascular disease in adults and chronic kidney disease [(25)]. In our study, the uric acid (UA) levels were significantly higher in males with DS than in the females DS, the reason of this finding is that, uric acid is the primary byproduct of purine metabolism. Hyperuricemia is associated with body mass index (BMI) and sex [(26)]. As well as, a positively correlation between body mass index and creatinine concentrations has been described by **Radoje Milić et al.**[(27)] this finding explained our results of creatinine levels were significantly higher in males with DS (1.80±0.19 mg/dl) than in the females DS (1.37±0.19 mg/dl), (*P*<0.05).

Creatinine and uric acid levels were reported to be higher in Down's syndrome patients[(28)] that finding agrees with our results which showed that creatinine and uric acid mean levels in serum of DS patients were significantly higher than in controls (p<0.05). Also, **Khan and Majumder** [(29)], showed that, serum creatinine level has been found significantly higher in hypothyroid patients. So, hypothyroidism should be taken into account in patients presenting with chronic kidney diseases.

Conclusion: Through the results of measuring some hormones and biochemical parameters in the present study of Down syndrome patients compared to healthy subjects, it turns out that Down syndrome patients are more vulnerable to diseases than others, such as kidney failure, liver diseases, infertility and should be followed to keep under control.

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الاضطرابات الهرمونية و البيوكيميائية فى مرضى متلازمة داون فى مصر

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مقدمة: المتسبب فى متلازمة داون هو كروموسوم زائد فى رقم ٢١ وهو الاكثر شيوعا وقد ينتج عن ذلك تخلف عقلى وتشوهات خلقية عديدة.

الهدف من البحث: الغرض من هذه الدراسة هو القاء الضوء على اهمية الفحص والمتابعة لبعض الهرمونات وبعض التغيرات البيوكيميائية لمرضى متلازمة داون.

تم عمل التحاليل المعملية لاحد وثلاثين مريضا بمتلازمة داون فى سن البلوغ وقورنت النتائج بثلاثين من الاصحاء كمجموعة ضابطة . تم تجميع عينات الدم الصائم لتقدير مستوى هرمونات الثيروكسن الحر و TSHو FSHو LHو E_2 و التستسترون fTالحر وكذلك مستويات الكرياتينين وحمض البوليك والزلال.

النتائج: باختبار وظيفة الغدة الدرقية ثبت ارتفاع مستوى هرمون TSH فى متلازمة داون بالمقارنه للمجموعة الضابطة فى حين ان مستوى FT4اقل وكانت مستويات FSH , LHاعلى بكثير فى متلازمة داون ($p<0.05$) وكان مستوى الاستراديول فى الاناث من متلازمة داون اقل من الضوابط (11.61±2.28 pg/ml) و (31.18±2.71 pg/ml) على التوالى فى حين ان مستوى التستسترون الحر اعلى مقارنة مع الضابطة (2.71±0.66 pg/ml) و (1.2±0.37 pg/ml) على التوالى

و فى الذكور من متلازمة داون كان مستوى الاستراديول طبيعيا (11.33±1.04 pg/ml) فى حين ان مستوى التستسرون كان اقل مقارنة مع الضوابط (1.98±0.21 pg/ml) , (2.63±0.44 pg/ml) على التوالى وايضا مستويات حمض اليوريك والكرياتينين فى متلازمة داون اعلى بشكل واضح مقارنة مع الضوابط بينما كان مستوى الزلال منخفض ($p<0.05$).

الخلاصة: من خلال نتائج قياس الهرمونات والتغيرات البيوكيميائية فى هذه الدراسة لمرضى متلازمة داون بالمقارنة بلاصحاء اتضح انهم اكثر عرضة من غيرهم للامراض مثل امراض الكلى وامراض الكبد والعقم ويجب متابعتهم حتى يظلوا تحت السيطرة.