A STUDY OF HORMONE PROFILES IN CRITICALLY ILL PATIENTS: AN EVIDENCE FOR HYPOTHALAMIC SUPPRESSION

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SUMMARY: This study was undertaken to define hormonal (thyroid, gonadal and pituitary) changes in 25 critically ill Libyan male patients including acute myocardial infarction (AMI: 5 cases, age 45-62 years), congestive cardiac failure (CCF: 5 cases, age 44-56 years), respiratory failure (RF: 5 cases, age 34-48 years), acute renal failure (ARF: 5 cases, age 22-42 years), and diabetic ketoacidosis (DKA: 5 cases, age 35-60 years). Serum T_3, T_4, fT_4, TSH, testosterone (Test), LH, FSH and prolactin (PRL) were estimated by RIA technique in patients during acute illness, clinical recovery and follow up as well as in Control Subjects (CS). During acute illness T_3 levels in all the patients were significantly reduced compared to CS ($p<0.05$). T_4 levels were also significantly reduced in RF ($p<0.02$) and DKA ($p<0.05$) but remained unaffected in AMI, CCF and ARF ($p>0.05$). Despite low T_3 and low normal T_4 levels during acute illness, TSH level was not elevated suggesting suppression of its secretion due to critical illness. During recovery phase, T_3 and T_4 levels were raised to normality ($p<0.05$) with marked elevation of TSH level ($P<0.05$) suggesting recovery of hypothalamopituitary thyroid axis from stress inhibition of critical illness. The rise in T_3 and T_4 levels was observed to be related to the rise in TSH level suggesting that TSH may have an essential role in restoring T_3 and T_4 levels to normal during recovery from critical illness. During follow up, T_3, T_4 and TSH levels were within normal ranges ($p>0.05$). The fT_4 levels remained normal during various phases of illness. Serum TEST, LH and FSH levels were depressed significantly during the phase of acute illness ($p<0.05$) except that LH levels remained normal in CCF, ARF and DKA ($p<0.05$). During clinical recovery serum TEST, LH and FSH levels rose to normal suggesting existence of transient hypogonadotropic hypogonadism in critical illness. Serum PRL levels were very high during acute illness ($p<0.02$) which fell to normal levels during clinical recovery ($p>0.05$) except in case of RF suggesting suppression of tuberohypophyseal dopaminergic neuron system in critical illness. During follow up the hormone levels were observed to be within normal ranges ($p>0.05$). Therefore, the hormonal changes observed during the phase of acute illness in critically ill patients and suggesting hypothyroidism and hypogonadism were transitory in nature and taken as evidence for central suppression, most probably hypothalamic.

Key Words: Non-thyroidal illness, hypothyroidism, hypogonadism.

INTRODUCTION

In a variety of acute non-thyroidal illnesses, low circulating levels of thyroid hormones (T_3, T_4) without an associated elevation in serum TSH have been shown to occur in many studies (1, 3, 6). Although exact mechanism responsible for these changes and their significance is not known, these changes are significant enough to be predictors of mortality (15). Despite the high mortality usually associated with the low T_4 state, several investigators have reported recovery associated with transient but inconsistent rises in serum TSH (3, 6, 18). Several observations have raised the possibility of pituitary or hypothal-

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amic diseases contributing to the aetiology of the low circulating levels of T_3 and T_4 seen in some critical illness on the pituitary-thyroid axis have been extensively studied, there are less data available regarding gonadotrophins (LH, FSH) levels in critically ill patients. Some reports are available suggesting a good correlation between the severity of the illness and the magnitude of decline in serum testosterone level (14, 19). However, there has been no consensus regarding the site of lesion in critical illness whether central or peripheral (4, 13). The literature survey has shown that no work of this kind has been reported in Libyan patients. We have therefore evaluated 25 male Libyans admitted with various types of critical illness for the following serum hormones: triiodiothyronine (T_3), thyroxine (T_4), free thyroxine (fT_4), thyroid stimulating hormone (TSH), testosterone (TEST), leutinizing hormone (LH), follicle stimulating hormone (FSH) and prolactin (PRL) during phase of acute illness, clinical recovery and follow up.

MATERIALS AND METHODS

Patients

The present study was conducted with informed consent on 25 male patients admitted in the intensive care unit of 7th April Hospital, Benghazi, Libya with acute myocardial infarction (AMI: 5 cases, 45-62 years of age), congestive cardiac failure (CCF: 5 cases, 44-56 years of age), respiratory failure (RF: 5 cases, 34-48 years of age), acute renal failure (ARF: 5 cases, 22-42 years of age) and diabetic ketoacidosis (DKA: 5 cases, 35-60 years of age). During acute illness (first week of admission), 5 specimens from each patient were analysed for various hormones. During clinical recovery which varied from three to five weeks of admission, 6 specimens from each patient were subjected to hormone analyses. The sera analysed during acute and clinical recovery phase were randomly selected from the various specimens received in the laboratory for routine biochemical investigations and on the basis of clinical information. All the patients reported for follow up, 4-6 weeks after discharge, whence fasting blood specimens were taken from each of them for the estimation of basal hormone profile. The patients with known thyroid disease, receiving massive blood transfusion or having steroid and dapamine therapy were excluded from the study. The sera from 25 age-matched healthy males were also analysed to serve as the control group (CS).

Radioimmunoassay (RIA) of hormones.

The hormones were estimated by RIA technique using Amerlex-^{125}I kits of Amersham, England, except testosterone (TEST) which was estimated by Gama B-^{125}I testosterone kit supplied by IDS Company, Usworth Hall, Washington, Scotland. All the RIA kits were based on the principle of competitive binding assay. Each serum was subjected to duplicate analysis. Three level controls (low, normal and high) were incorporated with each assay. The intra-and inter assay coefficients of variation were 2.3% and 4.5% for T_3; 3.1% and 6.5% for T_4; 3,8% and 7.4% for fT_4; 3.5% and 7.8% for TSH; 2.5% and 5.4% for TEST; 6.1% and 11.2% for LH; 4.20% and 9.6% for FSH; and 3.7% and 6.7% for PRL respectively.

Statistical analysis

The statistical significance of the results was evaluated by Student's t-test.

RESULTS

The results of the analyses for T_3, T_4, fT_4 and TSH levels during various phases are presented in Table 1. During phase of acute illness T_3 levels in all the patient groups irrespective of the type of illness were significantly reduced compared to CS ($p<0.05$). The T_4 levels were also significantly low in RF ($p<0.02$) and DKA ($p<0.05$) but remained unaffected in AMI, CCF and ARF ($p>0.05$). The fT_4 levels were not affected during acute illness. Despite low T_3 and low or normal T_4 during acute phase, TSH levels remained normal ($p>0.05$). During clinical recovery,

Table 1: The serum T_3, T_4, fT_4 and TSH levels (Mean±SD) in critically ill patients and control subjects (CS).

		T_3 (nmol/L)			T_4 (nmol/L)			fT_4 (pmol/L)			TSH (ulU/ml)		
		I	II	III	I	II	III	I	II	III	I	II	III
Patients	AMI	0.8±0.1	1.8±0.2	2.2±0.3	88±9	113±14	123±12	20±4	21±4	23±4	3.6±0.4	6.7±0.7	4.2±0.5
	CCF	1.0±0.2	2.4±0.4	2.1±0.2	81±10	106±9	128±14	27±5	16±4	22±6	2.4±0.3	8.2±0.6	3.8±0.4
	RF	0.8±0.1	1.4±0.3	1.8±0.3	37±5	90±10	112±11	21±3	18±4	18±5	3.8±0.5	12.0±2.5	5.0±1.0
	ARF	1.1±0.1	1.4±0.3	2.1±0.4	80±8	108±11	120±12	26±7	20±3	19±4	2.8±0.4	7.1±1.0	3.4±0.5
	DKA	0.7±0.1	2.2±0.3	2.1±0.2	58±7	118±12	118±12	25±4	19±2	20±4	3.1±0.3	6.8±0.7	3.8±0.4
Controls (CS)		2.3±0.3			1.30±14			20±3			4.1±1.0		

I: Phase of acute illness. Mean±SD of 50 observations.
II: Recovery Phase. Mean±SD of 60 observations.
III: Followup. Mean±SD of 10 observations.
CS: Mean±SD of 50 observations.

T_3 and T_4 levels raised towards normality as compared to CS ($p>0.05$). However, serum TSH levels during recovery phase, irrespective of the type of illness, were significantly elevated as compared to CS ($p<0.05$). During follow up, serum T_3, T_4, fT_4 and TSH levels were within the normal range ($p<0.05$).

The effects of critical illness on the pituitary-gonadal hormone axis are shown in Table 2. The TEST levels in all patient groups were decreased compared to CS during acute illness ($p<0.05$) and were elevated to nearly control levels during clinical recovery ($p>0.05$). The LH levels during acute illness were significantly depressed ($p<0.05$) in cases of AMI and RF; but were not affected significantly ($p>0.05$) in cases of CCF, ARF and DKA. The FSH levels in all the patient groups were significantly depressed during acute illness ($p<0.05$). During clinical recovery both LH and FSH levels were raised to normal levels ($p>0.05$). During follow up TEST, LH and FSH levels were all observed to be within the normal ranges. The mean level of PRL in all patients was elevated compared to CS during acute illness ($p<0.02$), which fell to control levels during clinical recovery ($p>0.05$) except in RF where PRL levels were still significantly elevated ($p<0.05$). However, during follow up the PRL levles in all patients were within the control ranges ($p>0.05$).

DISCUSSION

Our findings of low serum total T_3 and T_4 levels without an associated elevation of serum TSH during acute phase of critical illness were consistent with previous reports (1,3,6). Although the exact physiological basis for low circulating levels of T_3 and T_4 in critically ill patients is at present unclear, it may represent a common metabolic adaptation by the body to a stressful state for protein-nitrogen conservation as is observed in chronic renal failure (7). It is possible that due to insufficient stimuli by TSH, as a result of central suppression in critical illness, enough T_4 was not available for conversion to T_3. Although we could not perform TRH stimulation test to ascertain the site of central suppression-pituitary or hypothalamic, some workers have reported evidence for pituitary hyporesponsiveness to TRH (11) while others showed evidence for hypothalamic suppression (5, 9). However pituitary hyporesponsiveness was observed in patients receiving high doses of exogenous corticosteroids and dopamine (2, 10) which was not the case with our patients suggested that fall in TSH in acute illnesses could be due to suppression at hypothalamic level. The rise in TSH level followed by increase in T_3 and T_4 levels observed during clinical recovery suggested that TSH may have an important role to play in restoring T_3 and T_4 levels to normal during recovery from critical illness. In our study on hormones of the pituitary-gonadal axis, we found that during acute illness serum LH and FSH levels were low or normal while serum TEST levels were grossly depressed in all types of critical illness suggesting hypogonadotropic hypogonadism. However, these hormones wer raised to normal level during clinical recovery suggesting that the hypogonadism was transitory in nature and could be due to central suppression in critical illness.

Table 2: The TEST, LH, FSH and PRL levels (Mean±SD) in critically ill patients and in control subjects (CS).

		Patients					Normal Subjects (CS)
		AMI	CCF	RF	ARF	DKA	
TEST (nmol/L)	I	4.5±0.6	6.2±0.8	4.3±0.5	7.0±0.7	7.3±1.1	20.0±4.0
	II	14.4±1.1	13.8±2.0	12.2±2.0	13.7±2.0	16.5±2.1	
	III	12.2±1.0	14.5±2.1	11.9±1.4	14.4±1.0	14.6±2.1	
LH (mlU/ml)	I	1.6±0.2	3.0±0.7	2.0±0.4	3.8±0.5	3.5±0.4	5.0±1.5
	II	4.1±0.5	6.4±1.0	5.8±0.7	7.4±1.2	6.8±1.0	
	III	3.7±0.3	5.9±1.1	5.3±0.6	7.3±1.1	7.2±1.0	
FSH (mlU/ml)	I	1.5±0.2	1.9±0.6	2.0±0.3	2.1±0.3	1.9±0.2	5.0±1.7
	II	3.1±0.4	7.3±1.2	4.8±0.8	7.2±2.0	6.7±0.9	
	III	2.9±0.4	6.2±0.8	3.9±0.6	6.7±1.0	6.9±0.8	
PROL (ng/ml)	I	16.0±3.0	14.0±1.0	18.0±2.0	13.0±1.0	12.0±1.0	7.0±2.0
	II	8.0±1.1	5.9±0.9	11.3±1.5	6.6±0.6	4.9±0.5	
	III	6.0±1.0	5.5±0.7	8.8±1.0	6.1±0.7	4.9±0.6	

I: Phase of acute illness. Mean±SD of 50 observations.
II: Recovery Phase. Mean±SD of 60 observations.
III: Followup. Mean±SD of 10 observations.
CS: Mean±SD of 50 observations.

The normal response to Gn RH stimulation test in such patients as reported by some workers (11, 19) suggests that there is inadequate hypothalamic stimulation of gonadotropes due to acute illness. The high PRL levels observed in the patients during phase of acute illness support the work of others suggesting involvement of hypothalamus in critical illness (11, 16). It is known that the predominant effect of hypothalamus on PRL secretion is that of tonic suppression, an effect mediated principally through dopamine secreted by the tuberohypophyseal dopaminergic neuron system. There is loos of this inhibitory action of dopamine in critical illness leading to hypersecretion of prolactin (12). Many workers have shown that increased endogenous opioid activity in stressful states act on enkephalin and opiate receptors in the hypothalamus leading release (8). Therefore, our findings suggest that a transient hypothyroxenemia and hypogonadism exist in critical illness due to central suppression at hypothalamic level. The role of replacement therapy in critical illness with hypothyroxenemia and hypogonadism is uncertain. Although some workers reported improvement in clinical picture after thyroxine therapy (1), it was difficult to conclude whether the improvement was due to replacement therapy or spontaneous recovery from critical illness. A double blind study is required to ascertain the role of replacement therapy in persistent hypothyroxenemia and hypogonadism in critically ill patients.

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