



Original Article

Role of Cortisol and Growth Hormone in the Development of Ketosis Resistance in Malnutrition Related Diabetic Mellitus

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Abstract

Malnutrition Related Diabetes Mellitus (MRDM), a separate clinical class of diabetes mellitus recognized by WHO Study Group on Diabetes Mellitus in 1985 exhibits peculiar metabolic characteristic of ketosis resistance. To explore the role of cortisol and growth hormone in the development of ketosis resistance, a cross sectional study was carried out involving 21 newly diagnosed MRDM patients, 19 NIDDM patients, and 16 age matched non-diabetic control at BIRDEM, Dhaka. MRDM patients presented with significantly lower Body Mass Index ($P < 0.001$) and significantly higher level of serum glucose ($P < 0.001$) in comparison to NIDDM and control subjects. The mean serum cortisol was significantly higher in MRDM and NIDDM subjects compared to that of control ($P < 0.05$). Therefore, regarding cortisol, MRDM patients behave exactly like NIDDM patients. The serum growth hormone levels were similar in MRDM, NIDDM and control subjects. So it can be suggested from the study that cortisol and growth hormone may not play any significant role in the development of ketosis resistance in MRDM patients.

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Introduction

Diabetes Mellitus (DM) is a syndrome characterized by chronic hyperglycemia and disturbances of carbohydrate, lipid and protein metabolism associated with absolute or relative deficiency of insulin secretion or insulin action¹. Malnutrition Related Diabetes Mellitus (MRDM) has been recognized as a separate clinical class distinct from IDDM and NIDDM by the WHO Study Group on Diabetes Mellitus in 1985². Malnutrition Related Diabetes Mellitus affect mainly the young subjects below the age of 30 years among the poor community in the tropical developing countries causing chronic ill-health and death³. MRDM

Subjects includes a characteristic clinical features such as lean body built, body mass index (BMI) less than 19, the patient present with moderate to severe hyperglycemia, lack of ketosis in the absence of stressful situation, requirement of large doses of insulin for metabolic control and patient usually gives a history of childhood malnutrition⁴. Studies in some Asian developing countries have shown a low prevalence of IDDM in comparison to that of Western countries⁵. In contrast, MRDM might constitute 30-70% of all cases of young onset diabetes in several developing countries⁶. A study in Bangladesh showed that more than 50% of young diabetic subjects in Bangladesh belong to MRDM class⁷. Another study showed that among

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1499 under 30 diabetic patients 809 (55.5%) were MRDM class⁸. MRDM patients show metabolic peculiarities which fall between those of IDDM and NIDDM thus hyperglycemia may be severe but rarely ketotic. The majority do not become ketotic despite stopping insulin treatment for a long period even when required large doses for glycemic control. Ketosis was absent even when MRDM patient was suffering from severe systemic infection.^{9,10} Like the MRDM patients reported in other countries, this group of diabetic patients in Bangladesh also showed characteristic ketosis resistance¹¹. The reasons for the absence of ketosis in MRDM subjects have not been completely elucidated. The role of cortisol and growth hormone in the development ketoacidosis in IDDM is well established but the role of these two hormones in the development of ketosis resistance in MRDM patients is not yet explored. The study was designed to compare the cortisol and growth hormone levels among MRDM, NIDDM and healthy control subjects in order to explain the etiology of ketosis resistance in MRDM patients.

Materials and Methods

A cross sectional study was carried out at “Under 30 Diabetic Clinic” of Bangladesh Institute of

Research and Rehabilitation in Diabetes, Endocrine and Metabolism (BIRDEM), Dhaka, from January, 1997 to June, 1997. A total forty newly diagnosed young diabetic subjects selected randomly and were grouped into MRDM (n=21), NIDDM (n=19) on the basis of WHO Study Group Criteria 1985. Sixteen ages matched non-diabetic healthy subjects as control were also included in the study. The patient suffering from acute or chronic diabetic complications, chronic kidney or liver diseases, gestational diabetes and smokers were excluded from the study. After taking written consent, clinical history was recorded in pre-designed questionnaire. Height in centimeters and weight in Kg were measured, and BMI was calculated. Fasting blood was collected from each subject and serum was separated. Serum was analyzed for estimation of glucose level by GODPAP method, serum cortisol by ELISA Technique and serum growth hormone by ELISA Technique. Using SPSS window package did all statistical analysis.

Results and Observations

The clinical characteristics of the different groups of study subjects were shown in the Table I. BMI was significantly lower in MRDM (P<0.001) as compared to NIDDM and Control.

Table-1: Clinical Characteristics of the study subjects

Study Groups	Number of Subjects	Age in Years (mean±SD)	BMI (mean±SD)
Control	16	25.1 ± 4.2	22.3 ± 1.7
NIDDM	19	25.7 ± 4.7	23.0 ± 3.2
MRDM	21	21.5 ± 4.2	16.2 ± 1.3 ^{a,b}

ANOVA (Bonferroni) test was done as the test of statistics with the significance level 0.05.

BMI=Weight in Kg/Height in square meter.

a Vs Control b Vs NIDDM c Vs MRDM

Table II. Showed the different biochemical measures of the study groups. The mean ± SD serum glucose levels were 4.7 ± 0.4, 15.1 ± 4.6, 23.4 ± 6.6 mmol/L in the control, NIDDM, and MRDM subjects respectively. The serum glucose concentration in MRDM and NIDDM were significantly higher in comparison to control (p<0.001). The MRDM group was more hyperglycemic as compared to NIDDM (P<0.01). The mean ± SD serum cortisol levels were 261 ±

57.8, 353 ± 84.6, 506 ± 96.4 nmol/L in the control, NIDDM, and MRDM Subjects respectively. The serum cortisol concentration in MRDM and NIDDM were higher than control, only MRDM group showed significant difference as compared to control (P<0.01). The mean ± SD serum growth hormone levels were 2.14 ± 0.24, 2.02 ± 0.31, 2.12 ± 0.26 ng/mL in the control, NIDDM, and MRDM groups respectively. The serum growth hormone levels were closely similar in MRDM, NIDDM

and control groups without statistical difference, the correlation between serum glucose and serum cortisol of all diabetic subjects was shown in

figure 1. There was a significant positive correlation between the cortisol changes and the changes in glucose in the diabetic study subjects.

Table-1: Clinical Characteristics of the study subjects

Study Groups	Number of Subjects	Serum Glucose mmol/L (mean±SD)	Serum Cortisol nmol/L (mean±SD)	Serum Growth Hormone mg/mL (mean±SD)
Control	16	4.7 ± 0.4	261 ± 57.8	2.14 ± 0.24
NIDDM	19	15.1 ± 4.6 ^a	353 ± 84.6	2.02 ± 0.31
MRDM	21	23.4 ± 6.6 ^{a,b}	506 ± 96.4 ^a	2.12 ± 0.26

ANOVA (Bonferroni) test was done as the test of statistics with the significance level 0.05.

BMI=Weight in Kg/Height in square meter.

a Vs Control b Vs NIDDM c Vs MRDM

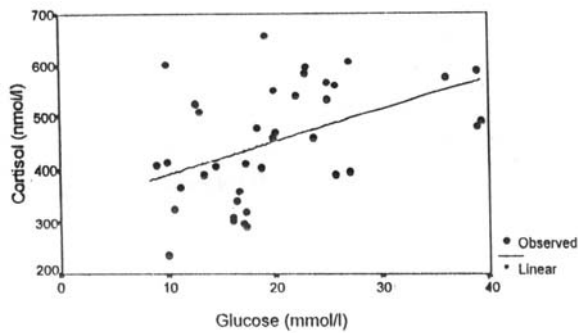


Fig. 9: Linear regression between serum glucose and serum cortisol of all diabetic subjects.

Discussion

Malnutrition related diabetes mellitus (MRDM), an insulin requiring, and young onset type of diabetes found in tropical developing countries including Bangladesh. These patients show a peculiar metabolic feature of ketosis resistance in the absence of stressful situation. Studies have shown that residual insulin secretion in MRDM patients might suppress ketogenesis^{11,12}. It has been postulated that ketone body metabolism is deranged in diabetes, where there may not be only diminished insulin secretion and action is responsible but also derangement in the secretion of other counter-regulatory hormones like cortisol and growth hormone are important factors for ketosis¹³. The role of cortisol and growth hormone in the development of ketosis in IDDM is well established but the role of these hormones in the development of ketosis resistance in MRDM, the role of these two hormones is worthwhile. The

present study was undertaken to investigate role of cortisol and growth hormone in the development of ketosis resistance by showing any changes in the level of these two hormones in MRDM patients. Forty newly diagnosed young diabetic subjects were selected randomly for this study at BIRDEM, Dhaka. The study subjects were grouped as per WHO guidelines into NIDDM and MRDM groups. Comparisons were made between sixteen healthy control subjects.

MRDM subjects in the study showed the characteristic clinical feature of lean body built, body mass index were less than 19 which were in agreement with other studies carried out by different researchers^{7,15}. It was also observed that MRDM patients present with very high level of fasting blood glucose ($P < 0.001$) compared to NIDDM and control as shown in table II. These findings were similar with those reported by other workers^{8,16}.

Regarding cortisol level, the both MRDM and NIDDM patients had higher cortisol values in comparison to control subjects. However, the MRDM class of diabetic patients had more higher level of serum cortisol as compared to control ($P < 0.01$). The levels of serum cortisol in the MRDM and NIDDM patients showed a strong positive correlation with the degree of hyperglycemia as measured by serum glucose ($r = 0.45$, $p = 0.01$). The positive correlation of serum cortisol with glucose in the diabetic subjects support the hypothesis that hypercortisolemia may

be an important contributing factor in the production of severe degree of hyperglycemia in the newly diagnosed MRDM and NIDDM subjects¹⁷. Therefore, from the study it is evident that cortisol levels in the MRDM patients behave exactly like that of young NIDDM patients. Although the excess of cortisol hormone plays an important role in the production of hyperglycemia as well as hyperketonemia in IDDM patients, the lack of ketosis in spite of severe hyperglycemia and elevated cortisol levels rules out the possibility of this hormone in the development ketosis resistance in MRDM patients.

The growth hormone concentration in MRDM patients did not differ from the control and young NIDDM patients. Since increased level of this hormone has been reported in newly diagnosed diabetic patients it may be tempting to hypothesize that the lack of increased growth hormone may be linked to the absence of ketosis in MRDM patients. However, study had shown that growth hormone also remain unchanged in insulin deficient diabetic patients¹⁸. Growth hormone is known to have a relatively less important role in the ketosis response of diabetic patients¹⁹. Thus, the ketosis resistance of MRDM patients may be attributable to the normal growth hormone levels. So it can be suggested from the present study that cortisol and growth hormone may not play any significant role in the development of ketosis resistance in MRDM patients. Although the present study excludes the possible involvement of the two stress hormones in the ketosis resistance of MRDM subjects in the basal state, it can not make any conclusion about the situation in the stimulated state when the availability of the ketogenic fuel (NEFA) is increased. Also other stress hormone like glucagon and epinephrine need to be studied for elucidation of ketosis resistance in MRDM patients.

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