

# Insulinoma in Saudi Arabia: A Twenty-Year Hospital Study

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## SUMMARY

The study was designed to assess retrospectively clinical pattern of insulinoma at a national referral center in the Kingdom of Saudi Arabia. All cases of insulinoma recorded at King Khalid University Hospital Riyadh between January 1987 and December 2006 were reviewed. During the 20-year period five patients were seen comprising three females (ages 38, 40, and 70 years) and two males (17 and 34 years). The duration of symptoms prior to diagnosis ranged between one and eight years. The commonest mode of presentation before diagnosis was inability to observe Ramadan fasting. Other notable symptoms included dizziness and loss of consciousness. All the five patients proceeded to operation. At surgery all were found to be benign tumors. Post-operatively, three of the patients developed pseudocyst, which resolved upon undergoing second surgery. Though clinical presentation of insulinoma in Saudi subjects is similar to those reported in the literature, our study revealed prominent symptoms occurring during yearly Ramadan religious fast could be a useful information in history taking. Further studies on a larger population are needed to further characterize our findings.

## KEY WORDS:

*Insulinoma, Clinical presentation, Saudi Arabia*

## INTRODUCTION

Insulinoma is known to be rare worldwide, with an incidence as low as below one per million person years to four per million<sup>1,2</sup>. The time from onset of symptoms to diagnosis also varies widely from 10 days to more than 20 years<sup>3,5</sup>. Patients with insulinoma often misdiagnosed as suffering from psychiatric or neurologic diseases and thus leading to further delay in reaching diagnosis<sup>6,8</sup>. Furthermore, symptoms of insulinoma in the form of hypoglycemia can be non-specific and at times subjects with the disease learn to avoid hypoglycemic symptoms by frequent feeding without seeking medical advice for prompt diagnosis<sup>9,10</sup>. Similarly, clinical presentation of insulinoma differs greatly ranging from weight gain on one hand to weight loss on the other<sup>3,9</sup>. Obviously, high index of suspicion is required for early diagnosis. Saudi Arabia being uniformly Muslim faith practicing yearly 29 or 30-day 12-hour fasting, it is not known if hypoglycemic symptoms occurring during the holy month of Ramadan would be useful in making diagnosis of insulinoma. In view of this, the study was set to determine retrospectively clinical features of Saudi patients with insulinoma who presented over 20-year period in order to help physicians make early recognition of the disease.

## MATERIALS AND METHODS

This study was conducted at King Khalid University Hospital (KKUH), Riyadh in Saudi Arabia. All hospital admissions were recorded using codes according to the international classification of diseases (ICD). Data of patients admitted at the hospital during the period 1987 to 2006 were retrieved from the record. KKUH is a teaching hospital of King Saud University Riyadh serving referrals from all over the Kingdom as well as local populace. All adult patients aged 12 and above admitted to the hospital with confirmed biochemical and/or histological diagnoses of insulinoma were included in the study. The following data were extracted from the patients' record: name, hospital number, gender, age at diagnosis and duration of symptoms before diagnosis. All patients had absent sulphonylurea in urine or plasma. Biochemical profile such as lowest blood glucose during 72-hour fasting with symptoms of hypoglycemia, along with corresponding plasma insulin and c-peptide levels were determined. Normal or high serum insulin level in the presence of low blood glucose with or without c-peptide suppression was diagnostic of insulinoma. Plasma insulin (uU/ml)/plasma glucose (mg/ml) ratio was calculated. A value of <0.4 was considered normal where as ratio >0.4 indicative of insulinoma. Pre-operative localization of the tumor was done using ultrasound, angiography and computerized tomography (CT) scan. Patients below 12 years were excluded from the study. Also excluded were patients who presented with symptoms of hypoglycemia but without biochemical and histological confirmation of insulinoma. Furthermore, subjects with inconclusive data were excluded from the study.

## RESULTS

This study was conducted at King Khalid University Hospital (KKUH), Riyadh in Saudi Arabia. All hospital admissions were recorded using codes according to the international classification of diseases (ICD). Data of patients admitted at the hospital during the period 1987 to 2006 were retrieved from the record. KKUH is a teaching hospital of King Saud University Riyadh serving referrals from all over the Kingdom as well as local populace. All adult patients aged 12 and above admitted to the hospital with confirmed biochemical and/or histological diagnoses of insulinoma were included in the study. The following data were extracted from the patients' record: name, hospital number, gender, age at diagnosis and duration of symptoms before diagnosis. All patients had absent sulphonylurea in urine or plasma. Biochemical profile such as lowest blood glucose during 72-hour fasting with symptoms of hypoglycemia, along with corresponding

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Table I: Patients Characteristics

Patient	Sex	Age	Clinical presentation	Duration (yrs)
A	Male	17	Dizziness	Not available
B	Male	34	Failure to fast Ramadan, dizziness, excess sweat	5
C	Female	38	Failure to fast Ramadan, convulsion	8
D	Female	70	Coma, aggressiveness, weight gain	2
E	Female	40	Failure to fast Ramadan, coma	1

Table II: Biochemical parameters in diagnosis of insulinoma

Patient	Blood glucose (mg/ml)	Insulin (uU/ml)	Insulin/glucose ratio	C-peptide (ng/L)
A	32.4	7.7	0.2	Not available
B	30.6	74.6	2.4	1.5
C	27	153	5.7	7.3
D	25.2	54.3	2.2	1.63
E	32.4	48	1.5	1.8

Table III: Patients management before and after surgery

Patient	Pre-operative care	Surgery	Post-operative complication	Histology
A	Diazoxide	Not available	Pseudo cyst	Not available
B	Parenteral dextrose	Enucleation	Pseudo cyst	Benign
C	Parenteral dextrose	Enucleation	None	Benign
D	Parenteral dextrose	Enucleation	None	Benign
E	Oral feeding	Enucleation	Pseudo cyst	Benign

plasma insulin and c-peptide levels were determined. Normal or high serum insulin level in the presence of low blood glucose with or without c-peptide suppression was diagnostic of insulinoma. Plasma insulin (uU/ml)/plasma glucose (mg/ml) ratio was calculated. A value of  $<0.4$  was considered normal where as ratio  $>0.4$  indicative of insulinoma. Pre-operative localization of the tumor was done using ultrasound, angiography and computerized tomography (CT) scan. Patients below 12 years were excluded from the study. Also excluded were patients who presented with symptoms of hypoglycemia but without biochemical and histological confirmation of insulinoma. Furthermore, subjects with inconclusive data were excluded from the study.

Table II shows the biochemical parameters used in diagnosis of patients with insulinoma. The lowest glycemia during fasting test was shown with corresponding plasma insulin and c-peptide levels. The average blood glucose level was 28.8 mg/dl (1.6 mmol/L) with a range of 25.2 mg/dl (1.4 mmol/L) to 32.4 mg/dl (1.8 mmol/L). All but one patient had plasma insulin level greater than 34 uU/ml. Furthermore, the plasma insulin/plasma glucose ratio was high in 4 of the 5 patients. Plasma c-peptide values were also shown. Only one patient had a plasma c-peptide above our laboratory cut off value for insulinoma of  $> 1.8$  ng/ml.

The dominant site of the pancreatic tumor was located on tail for all the patients. Two of the patients in addition had the tumor extended to the body of pancreas. Ultrasound of the abdomen detected the tumor in one of the five patients where as computerized tomography and arteriography detected the tumor in 2 and 3 of the patients respectively.

Table III shows pre- and post- operative management of the patients with insulinoma during the period of study. Four of the patients preoperatively had their symptoms of hypoglycemia controlled on either intravenous or oral glucose intake with or without diazoxide. One patient was

given diazoxide alone with adequate glycemic control. Detail of surgical management of patient A was not found although he was reported to have developed pseudocyst post-operatively. All the remaining four patients had enucleation of the tumor; two developed pseudocyst after recovery from the surgery. Histology report for all the four patients was reported as benign.

## DISCUSSION

We have confirmed insulinoma to be a rare tumor in Saudis. Throughout the two decades, only five adult patients were received in our hospital confirmed to have insulinoma. King Khalid University Hospital Riyadh being the referral center from all over the kingdom supported rarity of the disease in our local population. However, it is important to note that there is a limitation to such studies in general. Statistics derived from hospital figures are biased and are only approximate guide to the incidence of disease in a community. Many individuals, particularly in developing countries such as Saudi Arabia, do not attend hospitals at all<sup>11</sup>. What is seen in hospitals may represent only the tip of iceberg. The present data must be interpreted in the knowledge of the defects inherent in such studies. Nevertheless, the present data is in agreement with other observations in Caucasians, Asians, Turkish and African populations<sup>3, 12-18</sup>.

Insulinoma usually present with history suggestive of hypoglycemia, particularly when subjected to prolonged fasting. In this series, the occurrence of symptoms during the compulsory one-month half daily fasting in the month of Ramadan is a prominent feature of our study. Delay in diagnosis till the monthly fasting might be due to avoidance of hypoglycemic symptoms by having free access to food in the non-Ramadan months. The importance of including clinical history of inability or otherwise to observe daily religious fasting could not be over emphasized particularly in

our study population of an-all Muslim faith. Indeed, two of the patients had duration of symptoms prior to diagnosis for more than five years with complains of inability to complete Ramadan fast due to symptoms ranging from dizziness, excessive sweatiness to convulsions.

Although insulinoma may occur at any age, the frequently quoted mean age being between 45 and 55 years with a female predominance in western population<sup>18</sup>. In this study, we observed an average age at diagnosis of 40 years, in line with earlier observations elsewhere<sup>19-22</sup>. Admittedly, our data is too small to draw any meaningful statistical conclusion. However, despite this limitation, being a rare disease, it showed similar pattern as reported in other societies worldwide<sup>5, 13, 16</sup>.

Determining simultaneous plasma insulin and glucose levels at the time of clinical hypoglycemia has been shown to be crucial in confirming diagnosis of insulinoma. An inappropriately high serum insulin concentration in the presence of low blood glucose usually after prolonged fasting establishes the diagnosis. In this study, four of the five patients had high plasma insulin levels with corresponding low blood glucose levels. In addition, using plasma insulin/glucose ratio gave similar findings. However, only one patient had a high plasma c-peptide, others had normal or suppressed serum values. The normal serum levels of c-peptides seen in our study represent inappropriately high levels for the corresponding low blood glucose. Indeed, the test has been reported to be most useful in ruling out exogenous insulin than in confirming the diagnosis of insulinoma<sup>23, 24</sup>. Other tests such as stimulation tests were reported to be useful in diagnosis for some cases of insulinoma with associated risk of major hypoglycemic accidents<sup>20</sup>. Interestingly, stimulation tests were not used in our patients. Instead the subjects underwent 72 hour fast as previously described<sup>23</sup> and the test was conclusive in four of the five patients.

Pancreatic islet cell tumors are often small and hard to detect radiologically. Since these tumors are rare, comparing the accuracy of the various imaging tests is difficult. Nevertheless, sensitivity of ultrasonography in detecting insulinoma has been reported to be 9-63%, while MRI and angiography 16-72% and 36-91% respectively<sup>24, 25</sup>. Because MRI was introduced at our center lately, it was not used in the study. Despite this, the combination of CT scan and angiography showed to have a better detection value than ultrasonography with or without any of the two, in agreement with Ricke and Klose<sup>25</sup>.

## CONCLUSION

Our study confirmed insulinoma to be a rare disease in Saudi population. It also revealed an important data in history taking which we suggest should be emphasized in populations observing religious fasting in order to help diagnose insulinoma early and avoid its misdiagnosis. In view of the small number of patients further prospective studies are needed to verify our findings.

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