

# Insulinoma in a Saudi Arabian University Hospital: A Twenty-Year Review

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## SUMMARY

**Background:** Information on insulinoma in Saudi Arabia is lacking. The objective of the study was to review clinical features of the disease in a typical national referral center.

**Method:** In all, 5 cases of insulinoma were recorded at King Khalid University Hospital Riyadh Saudi Arabia between January 1987 and December 2006.

**Results:** During the 20-year period, there were 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 difficulty in observing Ramadan fasting due to intolerable hunger. 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, 3 of the patients developed pseudocyst, which resolved upon undergoing second surgery.

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## INTRODUCTION

Insulinoma is known to be rare worldwide, with an incidence as low as below 1 per million person years to 4 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 are often misdiagnosed as suffering from psychiatric or neurologic diseases thus leading to further delay in reaching a 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 of uniformly Muslim faith and practice 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 a diagnosis of insulinoma.

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In view of this, the study was set to determine retrospectively clinical and biochemical features of Saudi patients with insulinoma who presented in our hospital over a 20-year period in order to help physicians recognize the condition early.

## PATIENTS AND METHODS.

This study was conducted at King Khalid University Hospital (KKUH), Riyadh in Saudi Arabia. KKUH is a teaching hospital of King Saud University Riyadh serving referrals from all over the Kingdom as well as the local populace. 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. All adult patients 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 by electrochemiluminescence immunoassay (Roche Diagnostics, Indianapolis, IN, USA) with intra-assay and inter-assay coefficient of variation less than 2% and less than 3% respectively.

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 with inconclusive data or with symptoms of hypoglycemia but without biochemical and histological confirmation of insulinoma were excluded from the study.

## RESULTS

Of the 9 subjects reviewed, 5 patients satisfied the inclusion criteria for insulinoma during the 20-year period at KKUH Riyadh. Table 1 shows details of patient characteristics. Of the five patients, 3 were females aged 38, 40, and 70 years. The remaining 2 were males aged 17 and 34 years. The average age at presentation was 40 years. The commonly presenting symptoms of patients prior to diagnosis were inability to fast during the Muslim month of Ramadan due to intolerable hunger 60%, dizziness and loss of consciousness each representing 40%. One patient however came in with history of convulsion for 8

years (patient C) along with difficulties in fasting in the month of Ramadan. The duration of symptoms prior to final diagnosis of insulinoma ranged between 1 and 8 years with an average of 4 years.

**Table 2:** 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 are also shown. Only one patient had a plasma c-peptide above our laboratory cut off value for insulinoma of > 1.8 ng/ml.

**Table 3:** shows the pre- and post- operative localization of the tumors. The dominant site of the pancreatic tumor was located on the 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 5 patients while computerized tomography and arteriography detected the tumor in 2 and 3 of the patients respectively.

**Table 1: Patients Characteristics**

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

**Table 2: 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 3: Pre-operative localization of insulinoma**

Patient	Site	Ultrasound	CT Scan	Arteriography
A	Body + Tail	Not available	Not available	Positive
B	Body + Tail	Negative	Negative	Positive
C	Tail	Negative	Not available	Not available
D	Tail	Positive	Positive	Positive
E	Tail	Negative	Positive	Negative

**Table 4:** 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. Details of surgical management of patient A were not found although he was reported to have developed pseudocyst post-operatively. All the remaining 4 patients had enucleation of the tumor; two developed pseudocyst after recovery from the surgery. Histology was reported as benign in all the patients.

**Table 4: Patients management before and after surgery**

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

**DISCUSSION**

We have confirmed insulinoma to be a rare tumor in Saudis. Throughout the two decades, only 5 adult patients in our hospital were confirmed to have insulinoma. King Khalid University Hospital Riyadh being the referral center from all over the kingdom supports the 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 Caucasian, Asian, Turkish and African populations<sup>3,12-18</sup>.

Insulinoma usually presents with a history suggestive of hypoglycemia, particularly after prolonged fasting. In this series, the occurrence of symptoms during the compulsory daily one-month half-day fasting in the month of Ramadan is a prominent feature of our study. Delay in diagnosis until 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 complete half-day religious fasting as a result of severe hunger could not be over emphasized particularly in our study population of an-all Muslim faith. Indeed, two of the patients had symptoms prior to diagnosis for more than 5 years with complaints of unable to fulfill the religious obligation of Ramadan fast due to symptoms ranging from dizziness, excessive sweatiness to convulsions.

Although insulinoma may occur at any age, the frequently quoted mean age is between 45 and 55 years, with 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. Notwithstanding, our results showed similar pattern to that 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 the 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 correspondingly low blood glucose levels. In addition, using plasma insulin/glucose ratio gave similar findings. However, only one patient had a high plasma c-peptide while the others had normal or suppressed serum values. The normal serum level of c-peptides seen in our study represents inappropriately high level 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>25</sup> and the test was conclusive in 4 of the 5 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, the sensitivity of ultrasonography in detecting insulinoma has been reported to be 9-63%, while those of MRI and angiography are 16-72% and 36-91% respectively<sup>24-27</sup>. Because MRI was introduced at our center lately, it was not used in the study. Despite this, combination of CT scan and angiography was shown to have a better detection value than ultrasonography with or without any of the two, in agreement with Ricke and Klose<sup>27</sup>

In conclusion, our study confirms insulinoma to be a rare disease in Saudi population. It also revealed an important point in history taking which we suggest should be emphasized in populations observing religious fasting in order to help diagnose insulinoma early.

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