Glucose Tolerance Test in Beta-Thalassemia Major in Al-Sader City

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ABSTRACT:

BACKGROUND:

β-thalassemia are inherited defects in the synthesis of B-globin portion of hemoglobin. The combination of transfusion and chelating therapy has dramatically extended the life expectancy of thalassemic patients.

OBJECTIVE:

This study is to determine the prevalence of diabetes mellitus and association of some factors with impaired glucose tolerance test in transfusion dependent β- thalassemia major.

PATIENTS AND METHODS:

A case-control study done on patients attending blood disease center in Ibn-Al-Balady hospital from 1st of July to 31st of October 2011. Data collected from 287 thalassemic patients (being attended the hospital for regular follow up and blood transfusion) and their relatives which included age, sex, height, weight, history of splenectomy, family history of DM, hepatitis B or C infection, serum ferritin level and an oral glucose tolerance test.

RESULTS:

It was found that 9.7% of β- thalassemic patients had impaired glucose tolerance test and 1.1% were diagnosed with diabetes, 32.7% were splenectomized, 38.3% had viral hepatitis infection, mean serum ferritin in those older than 20 years was 5923±1033µg/l and 16.8% had family history of diabetes.

CONCLUSION:

Increased serum ferritin concentration, splenectomy and viral hepatitis infection are associated with abnormal glucose tolerance in patients with blood transfused b-thalassemia. Aggressive iron-chelating therapy and prevention and treatment of viral hepatitis infection were warranted.

KEY WORDS: β-thalassemia major, impaired glucose tolerance test, serum ferritin.

INTRODUCTION:

Beta Thalassemia (β-Thalassemia) represents a group of recessively inherited hemoglobin disorders first described by Cooley and Lee and characterized by reduced synthesis of β-globins chain[1]. The homozygous state results in severe anemia, which needs regular blood transfusion. The beta form of thalassemia is particularly prevalent among Mediterranean peoples. Far from the Mediterranean, North Africa, West and South Asia are also affected with the world's highest concentration of carriers (16% of the population) being in the Maldives[2,3]. The combination of transfusion and chelating therapy has dramatically extended the life expectancy of thalassemic patients who can now survive into their fourth and fifth decades of life [4,5]. Bone marrow transplants can be curative for some children with beta thalassemia major[6]. People with Thalassemia major can get too much iron in their bodies, either from the disease itself or from frequent blood transfusions. Too much iron can result in damage to heart, liver, spleen and endocrine system[7] which may cause hypogonadism, hypothyroidism, hypoparathyroidism and other endocrine abnormalities[8].

Insulin Dependent Diabetes Mellitus is a frequent complication mainly due to iron overload, chronic liver disease and genetic predisposition [9]. The diagnosis is based on measurement of HbA1C level, fasting or random blood glucose level, or oral glucose tolerance testing (OGTT) [10]. The OGTT can be used to diagnose diabetes, pre-diabetes, and gestational diabetes. OGTT measures blood

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glucose after a person fasts for at least 8 hours and 2 hours after the person drinks a liquid containing 75 grams of glucose dissolved in water[11].

The National Diabetes Data Group (NDDG) in the United States and World Health Organization (WHO) established diagnostic criteria in 1979 and updated in 1999 for normal glucose tolerance and diabetes based upon an oral glucose tolerance test (OGTT) (table no.1) [12].

Normal fasting plasma glucose (measured before the OGTT begins) should be below 6.1 mmol/L (110 mg/dL). Fasting plasma glucose less than 7.0 mmol/L (126mg/dl) and 2-hour plasma glucose level more than 7.8 mmol/L (140mg/dl) indicate impaired glucose tolerance. Fasting plasma glucose more than 7.0 mmol/L (126 mg/dL) and 2-hour plasma glucose level more than 11.1 mmol/L (200 mg/dL) confirm a diagnosis of diabetes (table no.1) [13,14,15].

Table no.1: Interpretation of Oral Glucose Tolerance Test and Diabetes criteria by WHO and National Diabetes Data Group (NDDG).

Glucose levels	NORMAL		impaired fasting glycaemia (IFG)		impaired glucose tolerance (IGT)		Diabetes Mellitus (DM)	
Venous Plasma	Fasting	2hrs	Fasting	2hrs	Fasting	2hrs	Fasting	2hrs
(mmol/L)	<6.1	<7.8	> 6.1&<7.0	<7.8	<7.0	>7.8	>7.0	>11.1
(mg/dL)	<110	<140	>110&<126	<140	<126	>140	>126	>200

People with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT) have an increased risk of developing overt diabetes and atherosclerotic vascular disease, even if they do not develop diabetes [15].

PATIENTS AND METHODS:

A case-control study was performed prospectively in Ibn-Al Balady hospital in (Al-Sader city-BA-Rasafa) for the period extended from the 1st of July to 31st of October 2011. Data were collected from 287 thalassemic patients being attended the hospital for regular follow up and blood transfusion. A control in this research work was one of the patient's relatives.

The collected data included: age, sex, height, weight, history of splenectomy, family history of DM, screening for hepatitis B or C infection(by detection of hepatitis B surface antigen and Anti-hepatitis C antibody), serum ferritin level and an oral glucose tolerance test (measuring blood glucose after a person fasts for at least 8 hours and 2 hours after the person drinks a liquid containing 75 grams of glucose dissolved in water) was applied for all thalassemic patients and the control group and was standardized according to WHO criteria of diabetes .

STATISTICAL METHODS:

Data were analyzed using Statistical Package for Social Science (SPSS) program for Windows version 20 to generate the general characteristics of the study. Quantitative variables were summarized by finding mean ± SD. Statistical analysis Differences between patients with and without abnormal glucose tolerance and between patients and control were tested with the independent t-test, x2 test and C-test to identify the potential risk factors. A two-tailed P-value less than 0.05 was considered to be statistically significant.

RESULT:

Table no. 2 shows that thirty five patients (12.1%) were 10 years old and less. One hundred thirty one patients (45.7 %) were more than 10 to 20 years old. One hundred twenty one patient (42.2%) were more than 20 years old. 13.3% of the control people were 10 years old and less. 40.1% of the control were 10years old to 20. 46.6% of the control were more than 20 years old.

Table no.2: Age of the thalassemic patients and control.

Age (year)	Thalassemic patients No. %	Control No. %
≤ 10	35 12.1	38 13.3
>10-20	131 45.7	115 40.1
>20	121 42.2	134 46.6
Total	287	287

Figure no. 1 shows that one hundred fifty two patients (52.9%) were females and one hundred thirty five (47.1%) were males. Control persons 62.1 % were females and 37.9% were males.

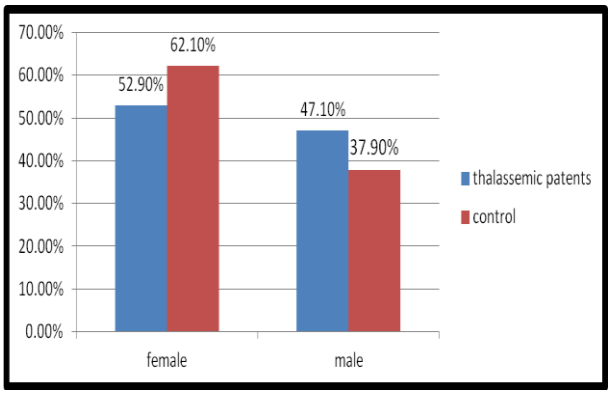

Figure no. 1: Sex distribution of the thalassemic patients and control.

Table no.3 shows that 5 thalassemic patients (13.1%) whose ages were 10 years old and less were splenectomized, thirty six patients (31.3%) whose ages were 10 to 20 years old were splenectomized and fifty three patients (39.5%) whose their ages more than 20 years were splenectomized. Ninety four patients (32.7%) of all the thalassemic patients were splenectomized.

Table no. 3: Splenectomized thalassemic patients.

Age (years)	Splenectomized No.	%	Non splenectomized No.	%	Total No.
≤10	5	13.1	33	86.9	38
>10-20	36	31.3	79	68.7	115
>20	53	39.5	81	60.5	134
Total	94	32.7	193	67.3	287

Figure no. 2 shows that 48 of the thalassemic patients(16.8%) and control had +ve family history of diabetes

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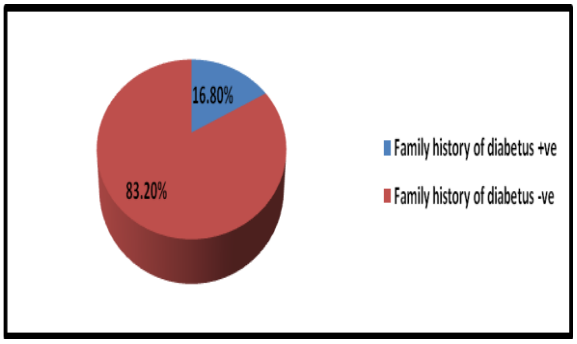

Figure 2: Relative distribution of +ve family history of diabetes in thalassemic patients and control.

Figure no.3 shows that 17(54.8%) of the thalassemic patients with abnormal GTT have +ve family history of diabetes and 14(45.2%) patients have no family history of diabetes. Thirty one (12.1%) thalassemic patients with normal GTT have +ve family history of diabetes and 225 (87.9%) patients have no family history of diabetes.

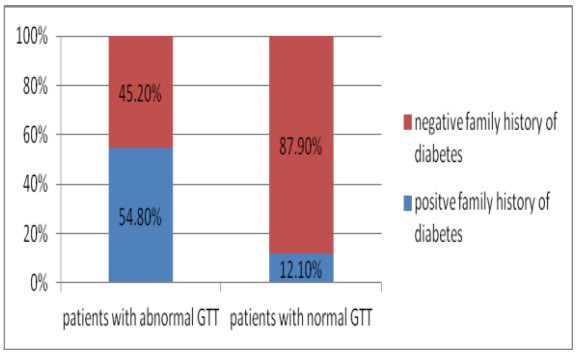

Figure 3: Relative distribution of +ve family history of diabetes in thalassemic patients with normal and abnormal GTT.

Figure no. 4 shows that 8.1% of the thalassemic patients were infected with hepatitis B, 26.4% were infected with hepatitis C and 3.8% were infected with both viruses. 61.7% of the thalassemic patients were not infected with hepatitis viruses (B&C).

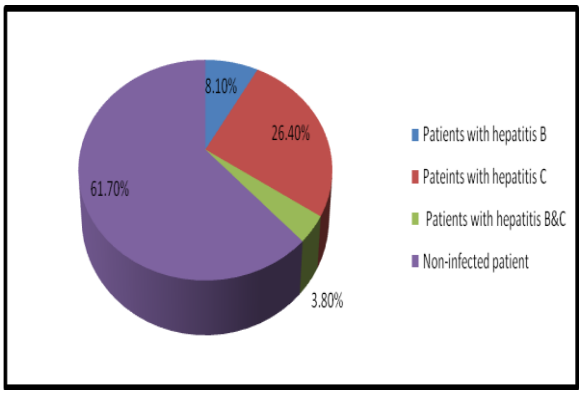

Figure 4: Relative distribution of the thalassemic patients with hepatitis B and C infection.

Table no.4A shows that thalassemic patients older than 20 years old were more liable for hepatitis viruses infection (p value =0.001<α= 0.05).

Table no. 4A: Thalassemic patients with hepatitis B and C infection.

Age (years)	Hepatitis B infection No.	%	Hepatitis C infection No.	%	Hepatitis B &C infection No.	%	Non-infected No.	%	Total No.
≤10	0		3	8.6	0		32	91.4	35
>10-20	5	3.8	28	21.3	3	2.3	95	72.6	131
>20	18	14.8	45	37.1	8	6.6	50	41.5	121
Total	23	8.1	76	26.4	11	3.8	177	61.7	287

Table no.4B shows that one of the controls (0.3%) was infected with hepatitis B and 3 of all the control (1.1%) were infected with hepatitis C.

Table no. 4B: Hepatitis B and C infection of the control.

Hepatitis B infection No.	%	Hepatitis C infection No.	%	Hepatitis B &C infection No.	%	Non-infected No.	%	Total No.
1	0.3	3	1.1	0		283	98.6	287

Table no. 5 shows mean serum ferritin in thalassemic patients who's their ages 10 years old and less was 3117±963 µg/L. Mean serum ferritin in those who's their ages older than 10 to 20 years old was 5167±1824.5µg/L and mean serum ferritin was 5923±1033.8 µg/L in those who were older than 20 years old.

Table no.5: Serum ferritin in thalassemic patients.

Age (years)	Mean of serum ferritin(Y) µg/l	Confidence Interval of the average serum ferritin (95%) $Y \pm t_{0.05/2}\ \sigma_{n-1}/\sqrt{n}$
≤10	3117	3117±963
>10-20	5167	5167±1824.5
>20	5923	5923±1033.8

Table no.6 A shows that none of the thalassemic patients who's their ages 10 years old and less had abnormal glucose tolerance test (GTT). Six patients (4.6%) whose their ages more than 10 to 20 years old had abnormal GTT and 1 of them was diagnosed with diabetes by GTT. Twenty five patients (20.8%) whose their ages more than 20 years old had abnormal GTT and 2 of them were diagnosed with diabetes. 10.8% of all the thalassemic patient had abnormal GTT and 1.1% of them were diagnosed with diabetes.

Table no.6A: Glucose tolerance test (GTT) of the thalassemic patients.

Age (years)	Impaired GTT No.	%	Diabetic patients No.	%	Normal GTT No.	%	Total No.
≤10	0		0		35		35
>10-20	5	3.8	1	0.8	125	95.4	131
>20	23	19.1	2	1.7	96	79.2	121
Total	28	9.7	3	1.1	256	89.2	287

Table no. 6B shows that only 4 of the control (3%) who's their ages more than 20 years had abnormal GTT and one of them (0.8%) was diagnosed with diabetes by GTT.

Table no.6B: Glucose tolerance test (GTT) of the control.

Age (years)	Impaired GTT No.	%	Diabetic patients No.	%	Normal GTT No.	%	Total No.
≤10	0		0		38	100	38
>10-20	0		0		115	100	115
>20	3	2.2	1	0.8	130	97.0	134
Total	3	1.1	1	0.3	283	98.6	287

Table no. 6A and no.6B also shows significant difference in the risk of getting abnormal GTT in those their ages more than 10 to 20 years old with thalassemia than control (p value =0.0004< α=0.05) and also for those who were older than 20 years old (p value=0.009<α=0.05). Table no. 6A shows thalassemic patients who older than 20 years were more liable for getting abnormal GTT than those more than 10 to 20 years old (p value=0.03<α =0.05).

Table no.7 shows that patients with abnormal GTT were older than those with normal GTT (P value=0.03). Regarding sex, there were no significant difference between thalassemic patients with abnormal GTT and those with normal GTT (P value=0.9> α=0.05).Height and weight percentile of thalassemic patients with abnormal GTT were not significantly different from those with normal GTT (P value =0.9 and 0.08 respectively).

Mean serum ferritin in those with impaired GTT was 5162±1340 µg/L, mean serum ferritin was 7410±2534 µg/L in those with diabetes and was 3576±895 µg/L in the normoglycemic patients. Mean serum ferritin were higher in thalassemic patients with abnormal GTT than those with normal GTT (P value=0.02). Three thalassemic patients with impaired GTT were infected with hepatitis B, 24 p;atients were infected with hepatitis C and 1 patient was infected with both hepatitis B and C viruses. All of the thalassemic patients with diabetes were infected with hepatitis C virus. Normoglycemic patients, 20 patients were infected with hepatitis B virus, 49 patients were infected with hepatitis C virus and 10 patients were infected with both hepatitis B and C viruses. Regarding viral hepatitis infection, there were significant difference between thalassemic patients with abnormal GTT and those with normal GTT (P value =0.04). All the patients with impaired GTT and those with diabetes were splenectomized. Sixty three normogly-cemic patients (24.6%) were splenectomyized (P value=0.002). Fifteen patients with impaired GTT had family history of diabetes, two patients with diabetes had family history of diabetes and 31 normoglycemic patients had family history of diabetes . Family history of diabetes were associated with abnormal GTT (P value=0.002).

Table no. 7: Demographic characteristics of thalassemic patients who had abnormal GTT and those with normal GTT.

Normal GTT		Diabetes		Impaired GTT		Patients criteria	
17±6*		23±3*		20±4*		Age (years)	
135	52.7%	2	66.6%	15	53.5%	Sex	female
121	47.3%	1	33.4%	13	46.5%		Male
256		3		28			Total
160	62.5%	3		18	64.2%	Height	≤3rd percentile
78	30.4%	0		7	25%		>3rd -50th percentile
18	7.1 %	0		3	10.8%		>50th percentile
153	59.8%	3		22	78.6%	Weight	≤3rd percentile
84	32.8%	0		5	17.8%		>3rd -50th percentile
19	7.4%	0		1	3.6%		>50th percentile
3576±895*		7410±2534*		5162±1340*		Serum ferritin (µg/L)	
20	7.8%	0		3	10.7%	Hepatitis virus	B
49	19.1%	3		24	85.7%		C
10	3.9%	0		1	3.6%		B&C
177	69.2%	0		0			-ve
63	24.6%	3		28		+ve Splenectomy	
31	12.1%	2	66.6%	15	53.5%	Family history of diabetes	

*Mean(Y) ± confidence interval ($Y \pm t_{0.05/2}\ \sigma_{n-1}/\sqrt{n}$)

DISCUSSION:

Beta-thalassemia affect both female and male equally (52.9% of the patients were female and 47.1% were male) because beta thalassemia represents a group of autosomal recessive blood disorders [1, 16].

Table no.3 shows that 32.7% of thalassemic patients were splenectomized mainly those older than 20 years old (39.5%). In Iran, 48.6% of thalassemic patients who older than 15 years old were splenectomized[17] and in India, 47.4% of thalassemic patients who older than 18 years old were splenectomized [18]. Splenectomy eliminates the extra corpuscular mechanism responsible for the accelerated destruction of normal donor red cells in the patient's circulation. This represents a lasting improvement and accounts for an increased longevity of normal blood supplements and a striking reduction of transfusion requirements. Less blood was required to maintain at least as good, and at times improved, hemoglobin levels. Splenectomy promote the patient's well being[19] but insulin resistance and iron deposition in the pancreas increased in splenectomized patients [20].

Positive family history of diabetes was more common in thalassemic patients with abnormal glucose tolerance than those with normal glucose tolerance test (54.8% vs. 12.1% with P value=0.02). Family history of diabetes may predispose multiply transfused thalassemics to glucose intolerance[21]. A study done in Italy shows that 50% of thalassemic patients diagnosed with type 1 diabetes before age of 15 years old had family history of diabetes versus 18% of those diagnosed after 15 years old[22]. In Iran, only 8.7% of thalassemic patients had family history of diabetes and 16% of diabetic patients had a family history of type I or type II diabetes in their siblings, parents or grandparents[23] and in Taiwan, 28.6% of thalassemic patients with impaired GTT had family history of diabetes and 25% of those with diabetes[24]. It is still unclear whether diabetes in β-thalassemia major is related to genetic factors[24,25].

Percentages of Hepatitis B, C and both B and C infection in our thalassemic patients were 8.1%, 26.4% and 3.8% respectively. In the control patients the percentages were 1.1% for hepatitis C and 0% for both hepatitis B and combined infection(B and C infection). Hepatitis infection mainly in those older than 20 years old(p value =0.001). The thalassemic patients have high risk of infection with hepatitis B and C[26]. In USA hepatitis C infection was 5% for those younger than 15 years old and 45% for those older than 25 years old. In some developing countries, the rate of hepatitis C infection was reported to be 63.8% [26]. In India, 5.7% of thalassemic patients younger than 10 years were positive for HBsAg and 25% were positive for anti-HCV[27]. In Pakistan, 12.2% of thalassemic patients younger than 15 years old were positive for anti-HCV, 16.8% for those 15 to 50 years old and 23% for those older than 50 years old had hepatitis C infection[28]. In Iran, 10.6% of thalassemic patients younger than 15 years old were infected with hepatitis C and 1.5% infected with hepatitis B[29]. The whole population prevalence is less than 1% in Iran that is lower than that of the regional countries: 1.1% in Yemen, 0.9% in children to 1.8% in adult blood donors in Saudi Arabia, and 4% of blood donors and 3% of college students in Pakistan[29]. These differences in the percentages of hepatitis infection which was high in USA in comparison with developing countries depend on the accuracy of hepatitis screening programs[26].

Means of the serum ferritin in thalassemic patients in Ibn Al-Balady center were 3117±967µg/l in those 10 years old and younger, 5167± 1824µg/l in those 10 to 20 years old and 5923±1033 µg/l in those older than 20 years old. There were no significant relation between mean serum ferritin level and age (p value=0.09>α=0.05) . Mean serum ferritin were slightly higher to mean serum ferritin level in the near locality like in Pakistan, the mean serum ferritin level was 4236.6 ng/ml in thalassemic patients who their ages 10 to 15 years old [30]. In Thalassemia Center in Dubai- UAE, mean serum ferritin for thalassemic patients 10 to 20 years old was 2597.2 ± 1976.8 µg/l[31] and in Iran, mean serum ferritin level in those younger than 10 years old was 2664±1361 µg/l and in those older than 10 years old to 20 years was 3296±1362 µg/l and there was no significant relation between age and mean serum ferritin in the major thalassemia patients (P-value= 0.42)[23]. So there was no significant relation between meanwqse serum ferritin level and age but it affected mainly by poverty, low education level, inadequate provision of health care and poor chelating regime [32] that's why serum ferritin level differ from one area to another. An unexpected increase in serum ferritin level should prompt assessment for hepatitis, infections, or inflammatory conditions[33].

Glucose tolerance test in our study was show that 9.7% of the thalassemic patients had impaired results and 1.1% had diabetes mainly those older than 20 years old (p value=0.03<α=0.05). In the control cases 1.1% were had impaired GTT and one case was diagnosed with diabetes, thalassemic patients had higher risk than control when data of both groups were compared by P-value (p value=0.0004 <α=0.05). In Tehran, 8.7% of the thalassemic patients had history of diabetes with mean age of diagnosis was 15±3 years[23]. In UAE, 10.5% of thalassemic patients had impaired GTT with mean age was 15.4±7.6[34]. In China 8.5% of thalassemic patients had impaired GTT[35]. In Taiwan, impaired GTT was seen in 8.7% of thalassemic patients and 19.5% had diabetes with median age 15±4.5 years[25]. In HawlerThalassemia Center in Iraq, study done on 50 thlassemic patients their ages between 10 to 15 years old, 26% of them were diagnosed with impaired GTT and none had diabetes[36]. Abnormal GTT result was more common in those older than 13 years old and rarely in those younger than 10 years old[34].

In table no.7, patients with abnormal GTT were mainly older than 20 years old, no significant difference was seen between males and females in the prevalence of diabetes mellitus, both height and weight were mainly below 3rd percentile (64.2% and 78.6% of thalassemic patients were below 3rd percentile for height and weight respectively), higher serum ferritin in those with diabetes (5162±1340µg/l in those with impaired GTT and 7410±2534µg/l in those with diabetes), all of them infected with hepatitis virus, all of them were splenectomized and family history of diabetes was more common in those with abnormal GTT (P value=0.002).

In Taiwan, mean age of thalalassemic patients with impaired GTT was 16.6±4.9 years, mean serum ferritin was 5827µg/l, 42.9% were infected with hepatitis C and non with B, 28.6% were splenectomizes and 28.7% had family history of diabetes; mean age of the diabetic patients was 17.4 years, mean serum ferritin was 5299µg/l, 56.3% were infected with hepatitis C and non with B, 50% were splenectomized and 25% had positive family history of diabetes[24]. In Tehran, mean age for thalassemic patients with diabetes was 15±3 years, no significant sex difference was seen, mean serum ferritin level was 1519 ± 920 µg/l and 16% of diabetic patients had a family history of type I or type II diabetes[23]. A study done by Lana Salem et al in Hawler Thalassemia Center in Iraq, in which the age was not a risk factor for abnormal GTT, 69.2% of those with impaired GTT were splenectomized, 68% were infected with hepatitis C, 76% their height below 3rd percentile and mean serum ferritin was 7030±226 µg/l [36]. Results of previous studies goes with the results of our study.

CONCLUSION:

It was found that 10.8% of multi-transfused beta-thalassemic patients had abnormal GTT which is occurring because of decrease insulin secretion and insulin resistance . Age of the patients, family history of diabetes, serum ferritin, viral hepatitis infection and splenectomy were associated with abnormal GTT in thalassemic patients. Sex, height and weight had no significant relation with risk of abnormal glucose tolerance test.

So all the following points are recommended to decrease risk of diabetes in thalassemic patients and improve their lives:

1- Aggressive iron-chelating therapy and early initiation of desferrioxamine therapy to keep serum ferritin <2500ng/ml but target value of ≤1000ng/ml is recommended(37).
2- Use of new oral iron chelating drugs will improve the patients compliance and more control of the serum ferritin.
3- Prevention and aggressive treatment of hepatitis infection are important to decrease risk of diabetes.
4- Screening of the patients by GTT who mainly older than 13 years old to catch up the risky patients and treat them properly.
5- Splenectomy when done to the patients they need aggressive iron chelating programs.

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