# Glucose and Insulin Metabolism in Fatty Liver

*YAĞLI KARACİĞERDE GLİKOZ VE INSULIN METABOLİZMASI*

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## SUMMARY

*Alterations in glucose and insulin metabolism in liver cirrhosis was widely investigated in recent years. Yet, there has been no study about the glucose and Insulin metabolism in pure fatty liver. In this study, we investigated the latter subject by me.ans of intravenous glucose tolerance test (IVGTT) IVGTT, by administration of 0.3 gr/Kg-body weight dextrose as 50% Dextrose in water in 1 minute was performed on 10 patients with biopsy-proved fatty liver and 8 healthy subjects. Blood samples were obtained in basal state and after 1st, 3th, 5th, 10th, 20th, 30th, 40th, 50th, 60th minutes after completion of dextrose administration. Glucose and insulin measurements were performed on sera by methods of glucose oxidase (1) and radioimmunoassay (RIA) (2) respectively. Serum glucose levels were significantly elevated in the patients at 1st, 5th, 10th, 30th, 40th, 50th, 60th, minutes. In addition total insulin response was significantly higher in the patients in comparison to controls. Insulin levels were significantly elevated in patients at 30th, 40th, 50th, and 60th minutes. The differences in insulin response in the first 30 minutes were not significant. Seltzer's insulinogenic index (serum insulin [U/ml] serum glucose [mg/dl]) was also significantly elevated in patients at basal state and 40th, 50th, and 60th minutes after IV glucose administration.*

*It was concluded that glucose and insulin metabolism is impaired in patients with fatty liver without cirrhosis. Significant elevation in glucose levels may indicate impairment of glucose utilization in these patients. However, elevation of Seltzer's Index in basal state as well as at and after 40th minutes may indicate absolute increase*

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## ÖZET

*Kronik karaciğer hastalıklarında glikoz ve insulin metobolizmasındaki değişiklikler yoğun biçimde araştırılmıştır. Ancak, herhangi bir etyolojik neden saptanmayan pür karaciğer yağlanmasında glikoz ve insulin metabolizmasını araştıran bir çalışma mevcut değildir. Biz bu çalışmada idiyopatik karaciğer yağlanmasında glikoz ve insulin metabolizmasını intravenöz glikoz tolerans testi (İVG TT) ile araştırdık. Tanısı karaciğer biyopsisi ile konulmuş karaciğer yağlanması olan 10 hastaya ve sağlıklı 8 kişiye bazal kan numuneleri alınımını takiben 0.3 gr/Kg-vücut ağırlığı dekstroz %50, dekstrozun sudaki solüsyonu halinde 1 dakika içinde İV yolla verildi. İnfüzyon bitimini takibeden 1,3,5,10,20,30,40,50 ve 60. dakikalarda kan numuneleri alındı ve serumları ayrılarak glikoz ve insülin tayini yapıldı. Serum glikoz düzeyi glikoz oksidaz yöntemiyle (1), serum Immun-reaktif insülin (İRİ) düzeyi Radyoimmuntest, (Radioimmunoassay, RIA) yöntemiyle (2) ölçüldü. Karaciğer yağlanması olan hastalarda İVGTT'nde 1,5,10,20,30,40 ve 60. dk'larda ortalama serum glikoz değeri, sağlıklı kontrollere kıyasla anlamlı olarak yüksek bulundu. Buna karşılık karaciğer yağlanması olan hastalardaki total insülin cevabı da sağlıklı kontrollere kıyasla anlamlı olarak yüksekti. Karaciğer yağlanması olan hastalarda 30,40,50 ve 60. dakikalardaki serum insülin düzeyleri, kontrollere kıyasla, anlamlı olarak yüksek bulundu. Seltzer'in insülinojenik indeksi [serum insülin (U/ml)/serum glikoz (mg/dl)] hesaplandığında hastalardaki bazal indeks, ve 40, 50 ve 60. dakikalardaki indeks kontrollere kıyasla anlamlı olarak yüksek bulundu.*

*Sonuçta karaciğer yağlanması kişilerde siroz bulunmasa da glikoz ve insülin metabolizmasının bozulduğu anlaşılmaktadır. İVGTT'ni takiben karaciğer yağlanması olan hastalarda serum glikoz düzeylerindeki yükselmenin sağlıklı kişilere kıyasla anlamlı olarak yüksek olması her ne kadar bu hastalarda glikoz ütilizasyonunda bir bozukluk olduğunu düşündürüyorsa da, bazal ve İV yüklemeyi izleyen 40. dk ve sonrasında Seltzer'in insülinojenik indeksinin hastalarda sağlıklılara kıyasla anlamlı olarak art-*

*In Insulin levels In circulation. This may be a result of Impairment of insulin degradation in liver in the patients with fatty liver without cirrhosis as well as Increase of insulin secretion from the pancreas.*

Key Words. Fitly liver, Hyperinaulinemia, Insulin resistance, Impaired glucose toleranct, Intravenous glucose tolerance test (IVGTT)

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*mış bulunması bu hastalarda mutlak insülin düzeyinde de bir artış olduğunu ortaya koymaktadır. Bu, aynı zamanda, pür karaciğer yağlanmasında karaciğerde insülin degradasyonundaki bir bozukluğun veya pankreasdan insülin sekresyonunda bir artışın işareti olabilir.*

Anahtar Kelimeler: Karciğer yağlanması, Hiperinsülinemi, insüline direnç, Glikoz intoleransı, Intravenöz glikoz tolerans testi (İVGTT)

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Fatty liver is one of the most frequent liver diseases and is frequently diagnosed incidentally. Sometimes it remains undiagnosed. While predisposing factors, such as alcoholism, diabetes mellitus, obesity are found in some patients with fatty liver, in a significant number of patients, no underlying cause can be identified.

Fatty acids reaching the liver, mostly via the portal vein, are taken up by the hepatic parenchymal cells and some are deposited as triglycerides, whereas the rest are incorporated In VLDL and released into the circulation. An Increase in the fatty acid supply to the liver (excess intake and the adipose tissue as well, put the liver on a continous fatty acid burden), an increase of lipogenesis in the liver due to relative or absolute deficiency of insulin, or consumption of an excess amount of alcohol for a long time lead to fatty liver (3). Cushing's disease and acute fatty liver o pregnancy are examples for hormone-mediated fatty liver. Tetracycline and valproic acid, an antiepileptic agent, may cause fatty liver by interfering with the incorporation of fat into VLDL. Protein deficiency in malnutrition is another cause of fatty liver. These aside, no underlying condition can be found in some cases of fatty liver. In most patients with fatty liver, biochemical liver function tests (serum bilirubin, transaminases [AST(SGOT), ALT(SGPT)], alkaline phosphatase, gamma-glutamyl transpeptidase, serum albumin, and globulin levels) are in the normal range. Still, in a significant number of patients increases in transaminases which cannot be explained otherwise is detected. GGT is increased especially in those associated with chronic alcohol consumption. Rarely, serum bilirubin is found to be increased. Ultrasonographic (US) evaluation, most of the time, reveals either focal or diffuse increase in the echogenicity of the liver. In fact, in most of cases, the diagnosis is established incidentally during an US examination. Computerized tomographic (CT) examination is more sensitive than US in detection of fatty liver. Liver biopsy as is in most other liver diseases is the most sensitive and specific method in the diagnosis of fatty liver. In fatty liver, prognosis is usually benign. Should the aforementioned etiological conditions relieved the increased transaminase levels may return to normal. In some cases it proceeds to steatonecrosis and fibrosis and cirrhosis may be established but this constitute only a minority and the course is far more better than those caused by other etiologies.

It has been known for a long time that there are defects in the metabolism of glucose and insulin in cirrhosis (4-6). In studies done mostly on compensated cirrhotics, insulin resistance, especially in the muscle tissu is found (7,8). Blood glucose has two sources: one that is coming from foods, the other that produced by the liver. Glucose is taken up by the liver and other viscera by the muscular and adipose tissues, transformed into glycogen or metabolized through the equilibrium between these three processes (metabolization of, and transformation into glycogen of glucose received bly the foods, and hepatic glucose production). Insulin inhibits hepatic glucose production, on the other hand in peripheral tissues especially in muscle facilitates glucose uptake. In cirrhotics, basal insulin levels are slightly increased compared to normals, in response to oral glucose loading supraoptimal insulin levels are achieved, but glycemia still remains high compared to healthy controls. This study is original in three respects: 1) Patients who have only fatty liver, but not cirrhosis were evaluated, 2) no underlying cause which may in itself interfere with glucose and insulin metabolism can be identified in these patients, 3) to overcome morphological and hormonal factors of the intestine which may have influences in OGTT and to evaluate the early insulin resoponse to glucose loading IV instead of OGTT was performed.

## MATERIAL AND METHODS

10 patients with fatty liver and 8 healthy persons were Included in the study. Fatty liver was diagnosed by means of liver biposy in all patients. Characteristic microscopic appearance of macrovesicular steatosis is shown in Picture 1. All patients were HBsAg negative and none had diabetes mellitus, chronic alcoholism, hyperlipoproteinemia, obesity ["Body mass index (BMI)" was less than 25 in all the patients and controls] or malnutrition. Ultrasonographic examination revealed enhancement in liver echogenicity in all patients. 8 patients were male and 2 were female, with a median

Table 1. SEXES, AGES, and AIT(SGPT) levels of patients with fatty liver

| PATIENTS | SEX, AGE | ALT(SGPT)(U) |
|---|---|---|
| M.B | M, 27 | 122 |
| Z.K. | M, 43 | 74 |
| Ö.T. | M, 26 | 115 |
| K.A. | M, 30 | 86 |
| E.M. | F, 56 | 92 |
| M.D. | F, 34 | 52 |
| V.Ç. | M, 45 | 44 |
| D.Y. | M, 32 | 182 |
| O.T. | M, 35 | 62 |
| O.A. | M, 45 | 56 |
| Median (ranges) | 35 (26-56) | 80(44-182) |

(M: Male, F: Female)

age of 35(range 26-56). The sole abnormality in physical examination was hepatomegaly in all patients. SGPT levels of all patients were above the upper limit of normal reference values (median: 80 U, range: 44-182, upper limit of normal reference value: 40 U). Some features of the patients are shown in Table 1. All patients had normal serum bilirubin, alkaline phosphatase, albumin and globulin levels. 3 females and 5 males were included in the control group with a median age of 23(range, 19-24).

In performing IV glucose tolerance test, basal blood samples were obtained from both patients and controls fllowing a 12 hour pasting period. Then 0.3 grams/Kilogram-body weight dextrose was administered in 1 minute in the form of 50% dextrose solution in water. The patients and controls had been fed with at least 250mg of carbohydrates per day during the preceding 3 days of IVGTT. After the completion of infusion, blood samples were obtained in the 1st, 3rd, 5th, 10th, 20th, 30th, 40th, 50th and 60th minutes from the Teflon catheter that was formerly applied to the antecubital vein of the patients' non-infused arms.

Serum glucose levels were measured in the auto analyser (RA 1000 Technicon) with glucose oxidase method (1) and stated as mg/dl. Serum insulin levels were measured with RIA method (2) and stated as uU/ml.

Seltzer's insulinogenic index was calculated by dividing serum insulin levels (uU/ml) by serum glucose level (mg/dl) (9).

In each patient and control summation of basal and 9 post-IV glucose load serum insulin levels were obtainde and was stated as total insulin level.

Mann-Whitney U test was used in statistical analysis and p values lower than 0.05 were considered significant.

## RESULTS

No significant difference was found between patients and healthy controls in the aspect of basal serum glucose levels (92±6 vs 92+6 mg/dl). In the first minute following the infusion of 0.3 gr/Kg-boody weight dextrose, serum glucose levels of the patients with fatty liver (371±10mg/dl) were significantly higher than those of healthy controls (274±3 mg/dl) ($p<0.05$). Following 5th, 10th, 20th, 30th, 40th, 50th and 60th minutes serum glucose levels were also significantly higher in patients with fatty liver than healthy controls The difference between 3rd minute values was not statistically significant. Serum glucose levels obtained in the 60th minute after the completion of 0.3 gr/Kg-body weight dextrose infusion, were 147±2 mg/dl in the patients with fatty liver and 95+9 mg/dl in healthy controls ($p<0.05$). The course of serum glucose level profiles in patients with fatty liver and healthy controls in the post IVGTT period is shown in Table 2 and Figure 1.

No significant difference was found between basal serum insulin levels of the patients and healthy controls (17 vs 10 uU/ml). The 30th, 40th, 50th, 60th minustes insulin levels of the patients with fatty liver

Table 2. Serum glucose levels of patients with fatty liver and healthy controls in IVGTT

| | Serum Glucose Leven in IVGTT (mg/dl) (Mean±SD) | | |
|---|---|---|---|
| | Patients (n-10) | Conrols (n=8) | p |
| Basal | 92±16 | 92±26 | |
| I.Min. | 371±110 | 274±54 | <0.05 |
| 3.Min. | 300+59 | 247±54 | |
| 5.Min. | 297+43 | 230+65 | <0.05 |
| 10.Min. | 263+47 | 197±70 | O.05 |
| 20.Min. | 233+67 | 160±58 | <0.05 |
| 30.Min. | 200±58 | 135+53 | O.05 |
| 40.Min. | 180+51 | 115±44 | <0.05 |
| 50,Min. | 161+47 | 101±35 | <0.05 |
| 60.Min. | 147±42 | 95±29 | O.05 |

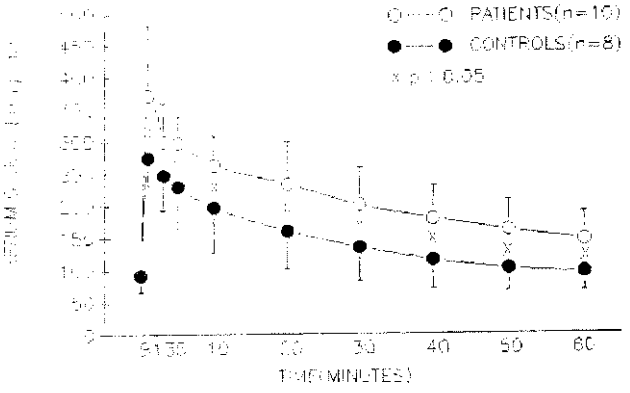



Figure 1. Serum glucose levels in patients with fatty liver and healthy controls in IVGTT (B:Basal)

**Table** 3. Serum insulin levels of patients with fatty liver, and healthy controls in IVGTT

| Serum insulin Levels in IVGTT OiU/ml) (MeantSD) | Patients (n=10) | Conrols (n=8) | p |
|---|---|---|---|
| Basal | 17±9 | 10±5 | |
| I.Min. | 67±36 | 58±35 | |
| 3.Min. | 87±50 | 58±39 | |
| 5.Min. | 77±33 | 63±39 | |
| 10.Min. | 78±33 | 46±33 | |
| 20.Min. | 68±33 | 35±24 | |
| 30.Min. | 62±31 | 28±23 | <0.05 |
| 40.Min. | 61 ±33 | 20+12 | <0.05 |
| 50.Min. | 54±32 | 16+11 | <0.05 |
| 60.Min. | 59±32 | 12±16 | <0.05 |
| Land 3.Min. | 155±75 | 115±74 | |
| Total | 634±184 | 351+110 | <0.05 |

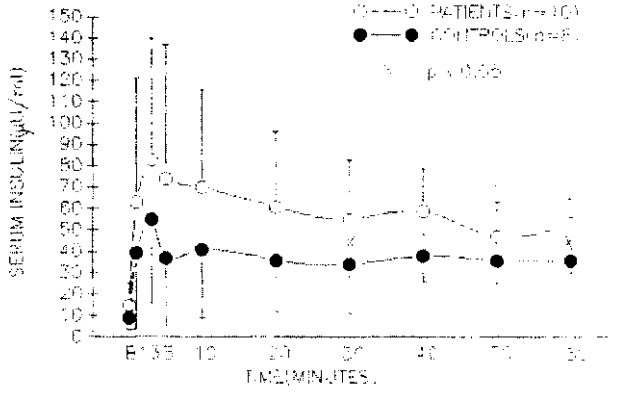



**Figure 2. Serum insulin levels of patients with fatty liver and healthy controls in IVGTT (BrBasal)**

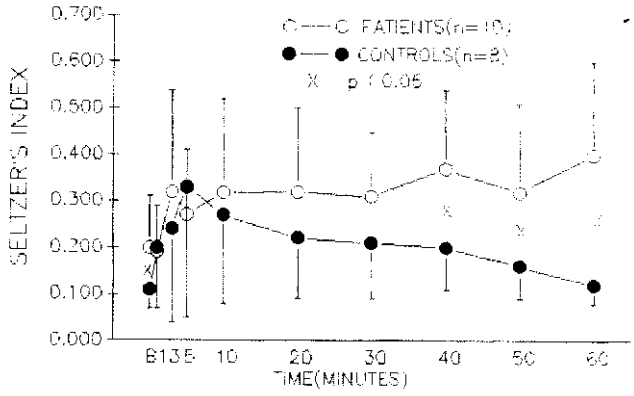



**Figure 3. Total serum insulin levels of patients with fatty liver, and healthy controls in IVGTT**

were significantly higher than those of healthy controls The 30th minute mean serum insulin level was 62±1 pU/ml in patients, while this value was found to be 12±16 mU/ml in healthy controls (p<0.05). Basal and post-IVGTT serum insulin levels are shown in Table 3 and Figure 2.

The summation of the 1st and 3rd minutes serum insulin levels revealed no significant difference between two groups (155±5 vs 115±4 pU/ml). Total insulin level was significantly higher in patients with fatty liver (634±184 fjU/ml) than that of healthy controls (351 ±10 pU/ml) (p<0.05) (Fig 3).

Seltzer's index which was obtained by division of serum insulin level (mU/ml) by serum glucose level was significantly higher than that of healthy controls in the basal samples (0.20±0.11 vs 0.11±0.04) (P<0.05). 40th, 50th, 60th minutes Seltzer's indexes were also significantly higher in patients with fatty liver. At 60th minute Seltzer's index was 0.40±0.20 in patients with fatty liver and 0.12±0.04 in healthy controls (p<0.05). Basal and post-IVGTT Seltzer's indexes are shown in Table 4 and Figure 4.

**Table** 4. Seltzer's indexes of patients with fatty liver, and healthy controls in IVGTT

| Seltzer's indexes in IVGTT (Serum insulin (pU/ml)/Serum Glucose (mg/dl) (Mean+SD) | Patients (n-10) | Conrols (n-8) | P |
|---|---|---|---|
| Basal | 0.20+0.11 | 0.11 ±0.04 | <0.05 |
| I.Min. | 0.19±0.10 | 0.20±0.13 | |
| 3.Min. | 0.32±0.22 | 0.24+0.20 | |
| 5.Min. | 0.27+0.14 | 0.33i0.28 | |
| 10.Min. | 0.32±0.20 | 0.27+0.19 | |
| 20.Min. | 0.32±0.18 | 0.22±0.13 | |
| 30.Min. | 0.31+0.14 | 0.21+0.12 | |
| 40. M in. | 0.37±0.17 | 0.20+0.09 | <0.05 |
| 50. Min. | 0.32±0.19 | 0.16±0.07 | <0.05 |
| 60.Min, | 0.40±0.20 | 0.12+0.04 | <0.05 |

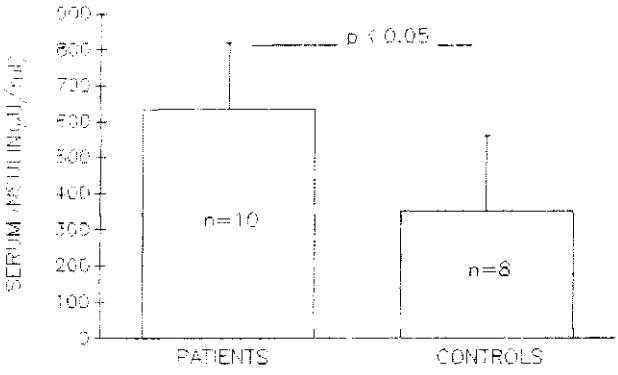



**Figure 4. Seltzer's indexes of patients with fatty liver and healthy controls in IVGTT (B: Basal)**

## DISCUSSION

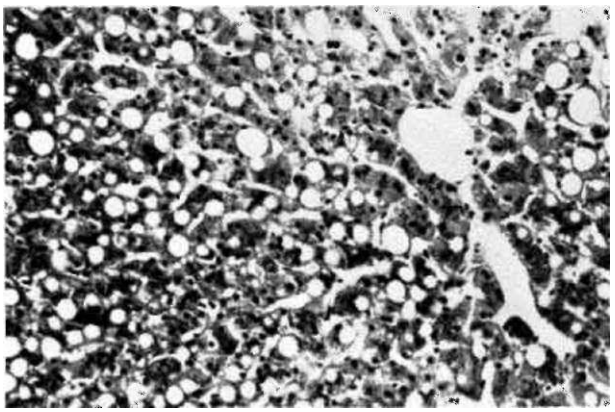
Many studies have been performed investigating glucose and insulin metabolism in liver cirrhosis. In most of them, the studied subjects were compensated cirrhotics. In these subjects, basal insulin levels were reported to be elevated. Oral glucose tolerance test (OGTT) reveals impaired glucose tolerance in these subjects despite exaggerated insulin response (10). Studies using euglycemic Insulin clamp technique which is the most reliable In evaluation of glucose and insulin metabolism showed that the major cause of the insulin resistance was impairment of utilizaiton of glucose by the muscles of these subjects and the process of conversion of glucose to glycogen was the main reason for this Impairment (9). The etiology of absolute hyperinsulinemia is claimed to be originated from altered degradation of this peptide by the liver. A significant drop in C peptlde/lnsulin ratio later OGTT supports the last hypothesis (8).

None of our studied subjects was cirrhotic. The studied patients with fatty liver were, in fact, constituting a subset of our patients of this kind. First, all of the patients showed elevated liver enzymes in serum which was taken as a point of justification in performing liver biopsy towards making a definitive diagnosis. In the case there are predisposing factors for fatty degeneration, the liver enzymes are in normal range and the results of the imaging techniques are compatible with this diagnosis, we are reluctant to perform biopsy. Second, none of the subjects had diabetes mellitus, malnutrition, alcoholism, or obesity which are likely to Impair the glucose and insulin metabolism. Therefore, the changes In glucose and insulin metabolism were thought to be specific of fatty liver in these subjects.

As it is seen at the 1st, 5th, 10th, 20th, 30th, 40th, 40th and 60th minutes following parenteral glucose administration, serum glucose levels were significantly elevated in the patients compared to healthy controls In addition the total insulin response of the patients against IV glucose load was significantly higher, compared to the response of the controls The insulin levels of the patients at 30th, 40th, 50th and 60th minutes following IV glucose load was also significantly elevated in comparison to the levels of healthy control subjects. Seltzer's index which is calculated as dividing the serum Insulin level by serum glucose level was found to be significantly elevated in patients at basal state and 40th, 50th and 60th minutes. The last finding may be taken as an evidence of absolute hyperinsulinemia in patients. The cause of this absolute hyperinsulinemia may either be impaired degradation by liver or increase in production by islet cells. The combination of both may also be possible. In the case the former hypothesis is true, it is interesting that pure macrovesicular stetosis impairs the handling of insulin by liver parenchyma. It may be speculated that simultaneous c-peptide measurement may have brought about more objective picture to the question of increased production or impaired degradation, because the degradation of this peptide which is produced in the same rate with insulin by pancreas is not impaired in liver cirrhosis. But, given to the erratic distribution pattern of this peptide in body, its value in such a discrimination was, recently, questioned (11).

These results show that there is an absolute hyperinsulinemia and impairment of glucose utilization in the patients with fatty liver. This is the first study showing this derangement in glucose and insulin metabolism In fatty liver. The most important factor regulating the glucose level in circulation after an glucose load is utilization of glucose by muscle mass. Although hepatic glucose production (HGP) and visceral glucose utilization also play some roles in this regulation, their contribution is minor in comparison to the former. In excluding the contribution of HGP, labelling of glucose by nuclear techniques may have been helpful. The fate of glucose in muscle is governed by two processes; metabolism and conversion to glycogen, Former studies showed that the disturbed mechanism in liver cirrhosis is the latter (9). Euglycemic insulin clamp technique may contribute greatly to the perspective in impairment of carbohyrate metabolism in fatty liven and it is really necessary to investigate these subjects by this method.

As it is seen even the exaggerated insulin response against IV glucose load in patients remains at relatively suboptimal levels, and insufficient in accomplishing the utilization of glucose by muscle mass. It was claimed that this suboptimal serum insulin level in respect to serum glucose level is a result of some strunctural dysfunctions in pancreas. It may be speculated that the increasing levels of serum free fatty acids may have an adverse effect on the uptake and metabolism of glucose by the liver. But, because we did not measure the levels of serum free fatty acids, it is not possible to comment further on this hypothesis.



**Picture 1.Macrovesicular steatosis**

In summary, patients with macrovesicular steatosis of the liver without any predisposing factors, such as diabetes mellitus, obesity, chronic alcoholism, toxic drugs or malnutrition, are found to have an insulin resistance characterized by hyperinsulinemia and glucose intolerance (Picture 1). In studying the patients with fatty liver with oral or intravenous glucose tolerance test, it may be useful to Include C-peptide and free fatty acid determinations as well. It must be remembered that, euglycemic insulin clamp technique is the most reliable method in evaluation of the impairment of glucose and insulin metabolism in these patients. Should, in addition to this technique, radiolabelling of administered glucose and measurement of metabolic activity of body by means of indirect calorimetry are done, it may be possible to bring about a clearer explanation to the mechanism of hyperinsulinemia and insulin resistance in pure liver steatosis.

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