Iron overload in kidney transplants: Prospective analysis of biochemical and genetic markers

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Background. The prevalence of iron overload and the influence of mutations in the HFE and TRF2 gene on biochemical markers of iron overload among renal transplant patients is unknown.

Methods. Serum iron, ferritin, transferrin saturation (TSAT), and liver function parameters were analyzed in a cohort of 438 renal transplants. In patients with iron overload, the time course of biochemical markers of iron status as well as the influence of iron loading mutations was investigated during a time period of 5 years.

Results. Of 438 renal transplant patients 41 (9.4%) presented with an iron loading phenotype (TSAT above 40% and/or ferritin above 800 ng/mL). Mutations in the HFE gene were present in 12 of 33 (36.3%) patients with iron overload. Among these one patient was homozygous for HFE C282Y, and two patients were compound heterozygous for HFE C282Y/H63D. No individual tested positive for nine other mutations in HFE as well as the TRF2 Y250X mutation. Over time we observed a decrease of mean iron and ferritin levels, and of mean TSAT in our study sample. In patients with mutations in HFE this decrease was less pronounced as compared to patients without mutations. We found an independent positive association between the presence of mutations in HFE and serum alanine-aminotransferase levels at follow-up (P = 0.003).

Conclusion. Our study demonstrates that iron overload is frequently present in renal transplant patients and shows a continuous decrease over time. This decrease is possibly impaired by the HFE C282Y and HFE H63D mutations. Furthermore, mutations in HFE may influence liver function as reflected by increased alanine-aminotransferase concentrations.

Iron overload refers to all conditions where excessive amounts of iron accumulate in the body ultimately resulting in parenchymal damage and organ dysfunction. Iron overload diseases can be due to inherited traits (primary iron overload) and/or acquired conditions (secondary iron overload) [1].

In recent years important insights into primary iron overload have emerged from studies of adult hereditary hemochromatosis. This is a genetically heterogeneous disease that is caused by mutations in at least two genes (HFE and TRF2) of iron metabolism [2, 3] and shows a late onset of iron deposition predominantly in the liver [4]. In patients with hereditary hemochromatosis continued absorption of iron occurs despite increasing body iron. Before significant amounts of iron are deposited in tissues, superfluous iron is released to the plasma followed by an increase of the transferrin saturation which is an early sign of developing iron overload [1]. As the years pass accumulating iron is stored in various tissues raising plasma ferritin levels. Thus, under normal circumstances transferrin saturation (TSAT) and the amount of circulating ferritin is related to the quantity of body iron stores [5]. However, serum ferritin and TSAT can be elevated out of proportion to iron stores limiting their value in diagnosing iron overload.

Important nongenetic factors contributing to iron overload (secondary iron overload) include iron supplementation and blood transfusions. Patients with renal insufficiency under different forms of renal replacement therapy are at risk for development of secondary iron overload for several reasons: First, before introduction of erythropoietin therapy for correction of renal anemia they frequently received blood transfusions on a regular basis. Second, since introduction of treatment with erythropoiesis-stimulating agents these patients routinely receive iron supplementation for successful treatment of renal anemia. Therefore, patients with renal insufficiency under different forms of renal replacement therapy represent a model to study the influence of genetic factors in an environment of secondary iron overload.

In the present study, we investigated biochemical markers of iron status and liver function over a time...
period of 5 years among stable renal transplant patients with an iron loading phenotype as defined by serum ferritin levels of more than 800 ng/mL and/or a TSAT above 40%. We also considered mutations in the \textit{HFE} and \textit{TRF2} genes.

**METHODS**

**Study design and patients**

The aim of the study was to investigate the influence of the \textit{HFE} and \textit{TRF2} genotype on biochemical markers of iron status and liver function over a time period of 5 years in a study population with biochemical signs of iron overload. Therefore a nested cohort study was designed. Patients were recruited from 438 stable kidney graft recipients. The detailed patient characteristics have been described previously [6]. Inclusion criteria were a phenotype of iron overload with a TSAT in serum above 40% according to the American Hemochromatosis Society (http://www.americanhhs.org) and/or a serum ferritin concentration of more than 800 ng/mL.

**Biochemical methods**

Blood chemistry was analyzed by standard methods. Serum iron, aspartate-aminotransferase (ASAT), alanine-aminotransferase (ALAT), gamma-glutamyltransferase (GGT), cholinesterase, C-reactive protein (CRP), and creatinine levels were measured using a Hitachi 747 analyzer (Roche Diagnostics, Mannheim, Germany). Serum transferrin concentrations were determined by the Behring Nephelometer II analyzer (Dade Behring, Liederbach, Germany). Serum ferritin levels were analyzed with a Hitachi 911 instrument (Roche Diagnostics). The prothrombin time (PT) was determined using the STA® coagulation analyzer (Roche Diagnostics). The TSAT was calculated by the formula serum iron (g/dL)/serum transferrin (mg/dL) × 70.9, respectively. The creatinine clearance was calculated using the equation of Cockcroft and Gault [7]. Hemoglobin levels and percentages of hypochromic red blood cells were analyzed with the Technicon H*2 hematology analyzer (Bayer Diagnostics, Tarrytown, NY, USA).

**Genotyping**

Mutation analyses were performed by reverse hybridization using the Haemochromatosis Strip\textsuperscript{a} assay A test system (ViennaLab, Vienna, Austria). This assay allows for simultaneous investigation of eleven mutations in the \textit{HFE} gene, including V53M, V59M, H63D, H63H, S65C, Q127H, E168Q, E168X, W169X, C282Y, and Q283P as well as the \textit{TRF2} X250Y mutation [8].

**Statistical analysis**

Continuous data are given as means ± standard deviation or as median and ranges. Categorical data are given as absolute counts and percentages.

We analyzed univariate associations of iron levels, of ferritin levels and of TSAT (at baseline and at follow-up) with age, gender, time since transplantation, time since initiation of renal replacement therapy, serum creatinine, estimated creatinine clearance, ASAT, ALAT, GGT, cholinesterase, PT, CRP, hemoglobin, and proportion of hypochromic red blood cells by Pearson’s correlation.

We compared paired and unpaired data by Student \textit{t} test.

Forward stepwise multiple linear regression models were established to examine independent predictors of TSAT, ALAT, ASAT, and GGT at follow-up. We included all variables in this model that showed a univariate association with iron level, ferritin level, or TSAT.

All analyses were performed using Statistica for Windows 5.1 (Stat Soft, Inc., 1997, Tulsa, OK, USA).

**RESULTS**

**Patients**

Of 438 renal transplant patients 41 (9.4%) fulfilled the criteria of iron overload. Eleven patients showed a TSAT >40% and a ferritin level >800 ng/mL, 16 patients showed a TSAT >40% but a ferritin level <800 ng/mL, and 14 patients had a ferritin level >800 ng/mL but a TSAT <40%. The baseline characteristics of all patients are shown in Table 1. During the follow up time of 5 years, eight patients died and one patient was lost for follow up. At this time point 15 patients showed biochemical signs of iron overload. Four patients showed a TSAT >40% and a ferritin level >800 ng/mL, seven patients showed a TSAT >40%, and four patients presented with a ferritin level >800 ng/mL.

**HFE and TRF2 mutations**

DNA for mutation analysis was available from 33 of the 41 patients. Mutations in the \textit{HFE} gene were present in 12 of 33 (36.3%) patients with iron overload. One patient was homozygous for \textit{HFE} C282Y, two patients were compound heterozygous for \textit{HFE} C282Y/H63D, two individuals were heterozygous for C282Y, and seven patients were heterozygous for H63D. None of the patients showed other mutations in the \textit{HFE} gene. Furthermore, no individual tested positive for \textit{TRF2} Y250X.
Time course of iron parameters according to HFE mutations

The time course of the biochemical markers of iron overload as well as the association of the HFE genotype with these markers was investigated in 33 patients. Among 21 patients without mutation, five individuals showed a TSAT >40% and a ferritin level >800 ng/mL, nine patients showed a TSAT >40%, and seven patients presented with a ferritin level >800 ng/mL at baseline. At follow-up two patients showed a TSAT >40% and a ferritin level >800 ng/mL, seven patients showed a TSAT >40%, and one patient presented with a ferritin level >800 ng/mL.

Among 12 patients with mutations in HFE, four individuals showed a TSAT >40% and a ferritin level >800 ng/mL, four patients showed a TSAT >40%, and four patients presented with a ferritin level >800 ng/mL at baseline. At follow-up two patients showed a TSAT >40% and a ferritin level >800 ng/mL, two patients showed a TSAT >40%, and one patient presented with a ferritin level >800 ng/mL.

The time course of indicators of iron overload for patients with and without mutations in HFE is shown in Table 2. We observed a decrease of mean iron levels, of ferritin levels, and of TSAT in our study sample. In patients with mutations in HFE this decrease was somewhat less pronounced as compared to patients without mutation in HFE (Table 2). Comparison of the difference of iron levels, of ferritin levels, and of TSAT between baseline and follow-up revealed a trend for a less pronounced decrease of iron parameters in patients with mutations in the HFE gene (Table 3).

The time course of the markers of iron status according to the different HFE mutations is shown in Table 4.

Independent predictors of the TSAT at follow-up are indicated in Table 5. GGT, ALAT, time since transplantation in years, creatinine clearance, and age were predictors of an iron loading phenotype after a follow-up time of 5 years. Hepatitis C infection was negatively associated with TSAT among iron overloaded patients (Table 5).

Time course of liver enzymes according to HFE mutations

The course of the liver enzymes in patients with and without mutations in HFE is indicated in Table 6. We observed no significant variation of liver enzymes during the observation period (Table 3). The liver function parameters according to the different mutations in HFE are given in Table 7.

Multivariate analysis revealed an independent positive association of hepatitis C infection (P = 0.04) and HFE mutations (P = 0.003) with ALAT. Furthermore, hepatitis C infection was independently associated with higher ASAT (P < 0.001) and GGT levels (P = 0.01).

Liver disease and mortality rates

None of the patients with mutations in HFE suffered from viral hepatitis. In contrast, hepatitis B or C infection was present in 7 of 21 patients without mutations in HFE (33%, one patient with hepatitis B and six patients with hepatitis C).

One patient died because of liver failure. This patient was homozygous for HFE C282Y. One patient presented with liver cirrhosis. This patient showed wild-type HFE alleles and suffered from a hepatitis C infection.

No case of alcoholic liver disease was documented among study patients.

Five-year mortality rates were 24% in patients without mutations in HFE, and 25% in patients with mutations in HFE.

DISCUSSION

The prevalence of iron overload was 9.4% among 438 long-term renal transplant patients. Thirty-six percent of cases with iron overload exhibited mutations in the HFE gene whereas the TRF2 X250Y mutation was not identified. Over time, we observed a less pronounced decrease of biochemical markers of iron overload in patients with mutations as compared to individuals without mutations.

A multiple stepwise regression analysis revealed that the presence of mutations in the HFE gene was significantly associated with TSAT among iron overloaded patients (Table 5).
Iron overload is present in 20.1% of long-term kidney transplant recipients and is attributable to occult blood losses, blood sampling, and low-meat dietary regimens [6]. By contrast, the prevalence of iron overload has been unknown. However, end-stage renal disease (ESRD) patients are at risk for iron overload as a consequence of red blood cell transfusions [5, 9] and intravenous injection of iron for correction of iron deficiency and renal anemia [10]. Among our study population 56% of patients were already maintained under renal replacement therapy before introduction of erythropoietin treatment and thus most of them had frequently received red blood cell transfusions because of persistent anemia. Thus, transfusional iron overload may explain iron overload in a large proportion of our patients.

Following introduction of recombinant human erythropoietin the prevalence of transfusional iron overload among ESRD patients decreased rapidly [11, 12]. Although erythropoietin is now widely used for correction of renal anemia iron overload still represents a possible complication because intravenous iron therapy is often required to maintain adequate iron stores for successful erythropoietin treatment [13, 14]. Among our 438 patients who had been transplanted almost 3 years ago 41 individuals still showed biochemical indices of iron overload although they had not received further iron supplementation. Other causes that could have contributed to the biochemical phenotype of iron overload in our patients include systemic inflammation, malignant disorders, and viral hepatitis. Among our renal transplants 17% showed evidence of a viral hepatitis, and 9% exhibited signs of systemic inflammation as reflected by elevated CRP concentrations in serum (3% of cases) and/or high ferritin levels and a TSAT below 15% (6% of cases). One patient (3%) suffered from lung cancer. Thus, in 29% of our patients the presence of a viral hepatitis, systemic inflammation or a malignancy could explain the biochemical signs of iron overload. Furthermore, excessive alcohol consumption can be associated with significantly higher serum ferritin, iron, and TSAT [15]. However, in
Transferrin saturation (TSAT) was elevated in a substantial number of patients. The mean age of the study population was 54.4 years, and because the patients were old enough to develop iron overload disease, the biochemical markers indeed could reflect the presence of tissue/organ damage. Whether or not the increased TSAT and hyperferritinemia indicate the presence of tissue/organ damage remains to be clarified since the presence of a systemic inflammation, and liver disease was observed in about 70% of our patients and because the patients were old enough to develop iron overload disease (mean age of the study population was 54.4 years), the biochemical markers indeed could reflect the presence of tissue iron overload (and thus tissue/organ damage) in a substantial number of patients.

Besides the before-mentioned causes genetic factors may predispose to iron overload. In apparently healthy individuals, heterozygosity, compound heterozygosity, and homozygosity for HFE C282Y and HFE H63D are associated with a significant higher TSAT in serum as compared to individuals with wild-type alleles [16–19]. The HFE S65C mutation possibly also influences TSAT, although this effect seems to be weaker as compared to HFE C282Y and HFE H63D [20, 21].

In the present study we have investigated 12 different iron loading mutations including the TRF2 Y250X that has been shown to result in a clinical phenotype comparable with HFE C282Y homozygotes [3, 4, 22–24]. In our study population only the HFE C282Y and the HFE H63D mutation have been found whereas HFE V53M, V59M, H63H, S65C, Q127H, E168Q, E168X, W169X, Q283P, as well as the TRF2 Y250X mutation were not identified. These data suggest that mutations other than HFE C282Y and H63D are not necessarily associated with iron overload in kidney transplant recipients.

During a time period of 5 years we observed a decrease of mean iron levels, of mean ferritin levels, and of mean TSAT among our renal transplant patients which is possibly attributable, at least in part, to the endogenous synthesis of erythropoietin by the donor kidney ultimately leading to mobilization of the iron stores for hemoglobin synthesis. Interestingly, in patients showing mutations in HFE this decrease was less pronounced as compared to individuals without mutations suggesting that recovery from secondary iron overload after renal transplantation is influenced by the HFE C282Y and H63D mutations. In our study all evaluated markers of iron status (i.e., serum iron, serum ferritin, and TSAT) decreased not as much as in patients with a mutation in HFE as compared to patients showing wild-type alleles. The greatest difference was observed for serum iron levels. However, these differences only showed borderline significance which might have been due to a too short follow-up. Of note the patient homozygous for HFE C282Y developed even an increase of serum iron and TSAT during follow-up suggesting that homozygosity for HFE C282Y can aggravate the time course of iron overload in renal transplant patients.

According to the Kidney/Disease Outcomes Quality Initiative (K/DOQI) guidelines of the National Kidney Foundation [25], the precise levels of TSAT or serum ferritin above which patients with chronic kidney disease will have iron overload is not known. In the present study we have chosen a TSAT above 40% as suggested by the American Hemochromatosis Society and/or a serum ferritin above which patients with chronic kidney disease will have iron overload is not known. In the present study we have chosen a TSAT above 40% as suggested by the American Hemochromatosis Society and/or a serum ferritin above which patients with chronic kidney disease will have iron overload is not known. In the present study we have chosen a TSAT above 40% as suggested by the American Hemochromatosis Society and/or a serum ferritin above which patients with chronic kidney disease will have iron overload is not known.

### Table 4: Time course of iron parameters in patients with different mutations in HFE (median, range in parenthesis)

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</thead>
<tbody>
<tr>
<td>Serum iron µg/dL</td>
<td>128 (125; 140)</td>
<td>132.5 (125; 140)</td>
<td>110.5 (81; 140)</td>
<td>103.5 (44; 163)</td>
<td>150.5 (92; 209)</td>
<td>283 (125; 1620)</td>
<td>68.4 (54.2; 82.6)</td>
<td>49.3 (36.2; 62.3)</td>
<td>32.5 (17; 43.5)</td>
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<tr>
<td>Ferritin ng/mL</td>
<td>933 (759)</td>
<td>634 (138; 1310)</td>
<td>332 (267; 397)</td>
<td>1195 (70; 2320)</td>
<td>873 (125; 1620)</td>
<td>843 (40; 1450)</td>
<td>873 (125; 1620)</td>
<td>843 (40; 1450)</td>
<td>873 (125; 1620)</td>
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<tr>
<td>Transferrin saturation %</td>
<td>57.1</td>
<td>82.7</td>
<td>53.2 (42.8; 63.6)</td>
<td>46.9 (38.3; 55.5)</td>
<td>53.2 (42.8; 63.6)</td>
<td>46.9 (38.3; 55.5)</td>
<td>53.2 (42.8; 63.6)</td>
<td>46.9 (38.3; 55.5)</td>
<td>53.2 (42.8; 63.6)</td>
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</table>

### Table 5: Independent associations with transferrin saturation (TSAT) in the year 2000 (follow-up of 5 years) in 33 renal transplant patients with iron overload (by multiple stepwise regression analysis)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>β coefficient</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Gamma-glutamyl-transferase 1995</td>
<td>0.407</td>
<td>0.01</td>
</tr>
<tr>
<td>Years since transplantation</td>
<td>0.388</td>
<td>0.04</td>
</tr>
<tr>
<td>Alanine aminotransferase 1995</td>
<td>0.605</td>
<td>0.006</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>–0.468</td>
<td>0.01</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>0.483</td>
<td>0.02</td>
</tr>
<tr>
<td>Age</td>
<td>0.422</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*P* < 0.00016; selection cut-off: F > 1, the variables follow the order in which they entered in the equation. Aspartate aminotransferase 1995, saturation of transferrin 1995, serum creatinine 1995, prothrombin time 1995, and serum ferritin 1995 were not significant.

None of our patients excessive alcohol consumption had been documented.

At this point, it must be considered that on the basis of increased serum ferritin concentrations it cannot be concluded that our patients suffered from iron-related tissue damage. We only have investigated the biochemical phenotype that can be influenced by factors others than those causing parenchymal damage and organ dysfunction. Whether or not the increased TSAT and hyperferritinemia indicate the presence of tissue/organ damage and thus is harmful for patients remains to be clarified (e.g., analysis of tissue iron concentrations). However, since the presence of a systemic inflammation, and liver disease could be excluded, the patients were old enough to develop iron overload disease (mean age of the study population was 54.4 years), the biochemical markers indeed could reflect the presence of tissue iron overload (and thus tissue/organ damage) in a substantial number of patients.

Besides the before-mentioned causes genetic factors may predispose to iron overload. In apparently healthy individuals, heterozygosity, compound heterozygosity, and homozygosity for HFE C282Y and HFE H63D are associated with a significant higher TSAT in serum as compared to individuals with wild-type alleles [16–19]. The HFE S65C mutation possibly also influences TSAT, although this effect seems to be weaker as compared to HFE C282Y and HFE H63D [20, 21].

In the present study we have investigated 12 different iron loading mutations including the TRF2 Y250X that has been shown to result in a clinical phenotype comparable with HFE C282Y homozygotes [3, 4, 22–24]. In our study population only the HFE C282Y and the HFE H63D mutation have been found whereas HFE V53M, V59M, H63H, S65C, Q127H, E168Q, E168X, W169X, Q283P, as well as the TRF2 Y250X mutation were not identified. These data suggest that mutations other than HFE C282Y and H63D are not necessarily associated with iron overload in kidney transplant recipients.

During a time period of 5 years we observed a decrease of mean iron levels, of mean ferritin levels, and of mean TSAT among our renal transplant patients which is possibly attributable, at least in part, to the endogenous synthesis of erythropoietin by the donor kidney ultimately leading to mobilization of the iron stores for hemoglobin synthesis. Interestingly, in patients showing mutations in HFE this decrease was less pronounced as compared to individuals without mutations suggesting that recovery from secondary iron overload after renal transplantation is influenced by the HFE C282Y and H63D mutations. In our study all evaluated markers of iron status (i.e., serum iron, serum ferritin, and TSAT) decreased not as much as in patients with a mutation in HFE as compared to patients showing wild-type alleles. The greatest difference was observed for serum iron levels. However, these differences only showed borderline significance which might have been due to a too short follow-up. Of note the patient homozygous for HFE C282Y developed even an increase of serum iron and TSAT during follow-up suggesting that homozygosity for HFE C282Y can aggravate the time course of iron overload in renal transplant patients.

According to the Kidney/Disease Outcomes Quality Initiative (K/DOQI) guidelines of the National Kidney Foundation [25], the precise levels of TSAT or serum ferritin above which patients with chronic kidney disease will have iron overload is not known. In the present study we have chosen a TSAT above 40% as suggested by the American Hemochromatosis Society and/or a serum ferritin concentration of more than 800 ng/mL as cut-off levels because our study population represented stable renal transplant patients. Using this threshold for iron overload we identified heterozygosity, homozygosity, or compound heterozygosity for HFE C282Y and HFE H63D in 36.3% of cases. This proportion is comparable with the prevalence of 31.4% reported among unselected hemodialysis patients from the same geographic era [26] as well as...
individuals of the general population of America and Europe [27], suggesting no major role of \textit{HFE} C282Y and \textit{HFE} H63D in the development of iron overload in renal transplant patients. Nevertheless, the above-mentioned threshold allowed identification of one individual homozygous for \textit{HFE} C282Y and two subjects compound heterozygous for \textit{HFE} C282Y and \textit{HFE} H63D suggesting high detection sensitivity.

In our study we observed no changes of liver enzymes in patients with iron overload without mutations in \textit{HFE}. In contrast, \textit{HFE} mutations were independently associated with ALAT levels. In this context, none of the patients showing mutations in \textit{HFE} suffered from viral hepatitis or excessive alcohol consumption suggesting an effect of mutations in \textit{HFE} on liver function in our study cohort. In this regard, an influence of the \textit{HFE} C282Y mutation on liver function tests (serum ASAT concentration) has been observed among individuals homozygous for \textit{HFE} C282Y [28].

Limitations to our study comprise the small sample size. However, all patients showing biochemical indices of iron overload of a large population of 438 renal transplant patients were included. Another limitation is that only mutations in \textit{HFE} and \textit{TRF2} have been analyzed. We did not test for other genes/mutations such as \textit{HAMP} [29–31].

**CONCLUSION**

Our study demonstrates that almost 10% of renal transplants show biochemical signs of iron overload even after 3 years of renal transplantation. During a further follow-up of 5 years all serologic markers of iron overload decreased. This decrease was ameliorated by the presence of the \textit{HFE} C282Y and \textit{HFE} H63D mutations. Moreover mutations in \textit{HFE} significantly influenced ALAT serum concentrations. Thus our study suggests a role of \textit{HFE} C282Y and H63D in the course of iron overload and liver function among renal transplant patients.

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**REFERENCES**


**Table 6. Time course of liver enzymes and prothrombin time (median, range in parenthesis)**

<table>
<thead>
<tr>
<th>Year</th>
<th>All patients ((N=41))</th>
<th>DNA available ((N=33))</th>
<th>Mutation ((N=12))</th>
<th>Wild-type ((N=21))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ASAT U/L</td>
<td>9 (5; 31)</td>
<td>9 (6; 31)</td>
<td>9.5 (7; 31)</td>
</tr>
<tr>
<td></td>
<td>ALAT U/L</td>
<td>9 (3; 47)</td>
<td>9 (3; 47)</td>
<td>9 (6; 28)</td>
</tr>
<tr>
<td></td>
<td>GGT U/L</td>
<td>17 (4; 922)</td>
<td>17 (4; 922)</td>
<td>22.5 (5; 922)</td>
</tr>
<tr>
<td>PT%</td>
<td>110 (61; 150)</td>
<td>122 (44; 150)</td>
<td>110 (61; 150)</td>
<td>110 (77; 150)</td>
</tr>
</tbody>
</table>

**Table 7. Time course of liver enzymes in patients with different mutations in \textit{HFE} (median, range in parenthesis)**

<table>
<thead>
<tr>
<th></th>
<th>282YY ((N=1))</th>
<th>282CY/63HD ((N=2))</th>
<th>282CY ((N=2))</th>
<th>63 HD ((N=7))</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASAT U/L</td>
<td>31 13</td>
<td>8.5 (8; 9)</td>
<td>12 (9; 15)</td>
<td>9 (7; 21)</td>
</tr>
<tr>
<td>ALAT U/L</td>
<td>28 12</td>
<td>10 (6; 14)</td>
<td>11.5 (6; 17)</td>
<td>9 (6; 15)</td>
</tr>
<tr>
<td>GGT U/L</td>
<td>922 347</td>
<td>66 (8; 124)</td>
<td>15.5 (9; 22)</td>
<td>24.5 (5; 115)</td>
</tr>
</tbody>
</table>

Abbreviations are: ASAT, aspartate-aminotransferase; ALAT, alanine-aminotransferase; GGT, gamma-glutamyl-transferase; PT, prothrombin time.

Abbreviations are: ASAT, aspartate-aminotransferase; ALAT, alanine-aminotransferase; GGT, gamma-glutamyl-transferase.

*One 282YY/C282Y genotype, two patients C282Y/H63D genotype; two patients heterozygous for C282Y; seven patients heterozygous for H63D.*