LIVER REGENERATION IN DONORS OF LIVER GRAFTS

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ABSTRACT

Liver regeneration after donor hepactectomy offers a unique insight into the process of liver regeneration in normal livers. Between June 2009 and October 2010, 40 live donor liver transplants (LDLTs) were performed in liver transplant unit in EL-Maadi armed forces hospital. All donors who provided liver grafts underwent volumetric spiral computed tomography scans preoperatively and postoperatively at time intervals of 1week and 1,3and 6 months. Patients' demographics, surgical data, and postoperative outcome were correlated with liver regeneration data. Thirty two males and eight females {mean age 27.97 $\pm$ 5.3} provided 36 right lobe grafts and 4 posterior sector grafts. No donor operation was aborted and surgical morbidity rate was 47.5%. Donor remnant liver volume was 47.1$\pm$5.2% of original total liver volume in RL donors and 63.7$\pm$4.8% in RT Post. Sector donors. Overall regeneration was 95.3% of TLV at 6 months. Donors of right lobe grafts and donors with small remnant liver volume had significantly faster liver re-growth more than the others. Also, female donors had significantly faster liver re-growth more than males and teenagers show slow regeneration than the other age groups at POD 7. There was no effect of operative time, steatosis, BMI, blood loss, blood transfusion, postoperative complications or perioperative liver function tests on liver regeneration. All posterior sector donors achieved complete liver regeneration after 3 months; only two RL donors achieved complete liver regeneration at 6 months. However all donors have maintained normal liver function without long-term complications.

Key wards: living donor, liver transplantation, regeneration, right lobe graft, right posterior sector graft.
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INTRODUCTION

Liver transplantation has had a profound impact on the care of the patients with end stage liver disease and is the most effective treatment for many patients with acute and chronic liver failure resulting from a Varity of causes.1

The growth and development of living donor liver transplantation (LDLT) has been rapid over the past 15 years.[2] Following the first successful report in 1989, LDLT became an acceptable modality to treat end-stage liver disease [3] and offers hope to

Numerous studies have addressed the extent of liver regeneration after partial hepatectomy for benigin and malignant tumours, but few have characterized hepatic regeneration in the healthy live donors.[8-10]

The aim of our study was to visualize kinetic of liver regeneration in adult living related donors, to estimate rate of growth of patients with end-stage liver disease in areas where the waiting mortality is high and the availability of deceased donor organs falls short of the population.[4]

Normal Liver regeneration is a complicated process dependent upon the activation of more than one hundred genes and involvement of numerous growth factors. [6] this process is highly effective, since, following hemi-hepatectomy and liver donation, the structure and function of the liver are largely restored after two or three weeks, and completely after six months.[7-9] remnant liver of donors and assess factors that might affect it.

PATIENTS AND METHODS

Between June 2009 and October 2010, surgical team in liver transplant unit in El-Maadi armed forces compound hospital performed 40 LDLT using right lobe grafts from 36 healthy donors and right posterior sector grafts " segment VI , VII " from 4

healthy donors. Twice weekly, a multidisciplinary screening committee composed of the members of the surgical team and internal medicine doctors met to review the recipient donor couple and evaluate the recipient risk, indication of transplant and other options if transplant is not indicated. The most common indications were liver cirrhosis 55% (22 patients) and HCC 25% (10 cases) caused by HCV infection.

Potential donors should be aged from 18-45yrs, donors over that age are excluded due to high risks on the donor and graft function. Potential donors should be related to the recipients. Potential donors are told of the details of indications for liver transplantation, the risk of donor and recipient morbidity and mortality, and alternative treatment of recipients. Living donors and recipients should have compatible blood groups. All the donor demographics are recorded regarding age, sex, weight, height, BMI, blood group , degree of steatosis , type of the graft, CT total liver volume , CT right graft volume .

All donors underwent liver function tests preoperatively and daily at the 1st week postoperative, then at 1, 3 and 6 months postoperatively. All donors underwent liver biopsy to exclude donors with macrovesecular steatosis more than 10%.

Liver US Duplex to assess the hepatic venous and portal anatomy was performed preoperatively then at day 1, 3, 7 postoperatively to exclude portal vein thrombosis or fluid collection. Then at 1, 3 and 6 months postoperatively, to detect the increase in the portal flow and presence or absence of portal hypertension.

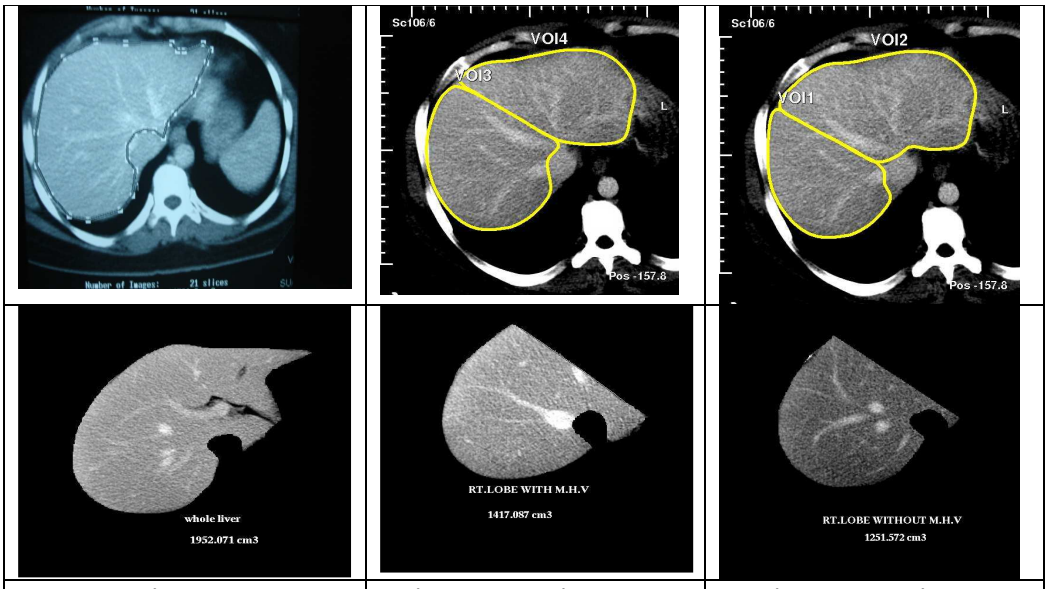
Multiphase abdominal computed tomography angiography (CTA) for determining liver morphology, volume, and vascular anatomy was performed preoperatively and 1week, 1,3and 6 months postoperatively to detect increasing ratio of regeneration.

The CT volumetry protocol used to assess donor liver volume, we used manual measurements to calculate liver volumes by hand-tracing the liver outline on the axial portal venous phase images. Hand-tracing was performed to isolate the liver from surrounding structures of similar attenuation, such as the stomach and spleen (Fig. 1). Hand-tracing was not performed with every axial image, but the frequency was dependent on the change in liver contour. On preoperative CT scans using hepatic veins as guidance, we measured the total liver volume; the volume of the right lobe of the liver; the remnant liver volume, which included the caudate lobe, segment IV, and bi-segment II + III. For the right lobe, a line parallel to the right side of the middle hepatic vein was drawn, and the circumference of the right side of the liver was marked manually in slices 1 cm thick. When the estimated liver remnant volume is less than 35%, the candidate, in principle, is considered unsuitable as a living donor. The GRWR has been used to assess the graft size of a potential donor, and values of less than 0.8% have been associated with increased post-transplantation mortality and morbidity.

Thirty six donors underwent right hepatectomy, the remained liver was the left lobe with preservation of the MHV in the donors. While in the four donors of right posterior sector graft, we took segment VI, VII with preservation of left lobe plus segment V, VIII in the donors.

All the operative details are recorded regarding the length of the operation, blood loss, autologous blood and FFP transfusion, actual right lobe graft weight, and posterior sector graft weight and donor remnant volume. All donor complications, defined as any unexpected or untoward event, were collected prospectively and recorded, both

minor and major complications were recorded. All donors were monitored for 6 months postoperatively for surgical, medical and psychiatric complication.



Total liver volume	Right lobe with MHV	Right lobe without MHV

Fig. 1: CT Volumetry Protocol.

Statistical analysis:

Donor remnant volume {DRV} was calculated as the estimated total liver volume {TLV} minus the actual graft weight {AGW}. Regeneration was expressed as a percent of the original TLV using follow-up computed tomography {CT} liver volume. Total liver volume by cm^3 was recorded at the time interval of follow-up. Increased ratio was calculated by this formula {reg. LV – DRV}/DRV* 100 as reg.LV was the new remnant liver volume at the time interval of follow-up and DRV was the remnant liver volume "the donor remnant volume at day 0".data are expressed as mean ± standard deviation. Person's correlation was used to analyze associations between two continuous variables. Statistic analyses were done using the statistical package for the social science {SPSS}. A p value < 0.05 was considered statistically significant.

RESULTS

Forty potentially living donors with compatible blood type were evaluated , thirty two (80%) male, eight (20%) female underwent hepatic resection for LDLT, thirty six (29 males and 7 females) represented (90%) of them underwent right hepatic resection with preservation of MHV in the donor and four (3 males and 1 female) represented (10 %) of all donors underwent right posterior sector "segment VI, VII "hepatic resection. Most donors were blood group O (47.5%), relatively young (27.97 ± 5.3years) and had normal body weight and height (Body mass index 25.2 ± 3.37). The preoperative liver volume measured by CT volumetry program was 1677 ± 225.3 cm^3 for right lobe graft and 1653.6 ± 187.1 cm^3 for right posterior sector graft. Multi-detector CT scan was excellent in predicting mean right lobe liver volume {predicted 957.8 ± 177.1 ml vs. actual 858.9 ± 165.3 g} P< 0.001 by paired t test. The actual mean

right posterior sector graft liver volume was 597 ± 104.8 g. Actual graft volume was 89.7 % of the CT predicted right lobe liver volume. The donor's remnant liver volume was 47.1± 5.2 % of TLV in right lobe and 63.7 ± 4.8 % of TLV in right posterior. The mean GRWR was 1.05%.

Table 1 donor's characteristics

	Number of donors
Sex:	
Male	**32**
female	**8**
AGE:	**27.97 ± 5.3**
10-20 yrs	**2**
21-30yrs	**25**
31-40yrs	**13**
BMI	**25.2 ± 3.37**
BLOOD GROUP	
A	**15 { 14"A+ve"- 1"A –ve" }**
B	**5 {4"B+ve"- 1"B-ve"}**
O	**19 "O +ve"**
AB	**1"AB +ve"**
Liver biopsy	
• **No steatosis**	**25**
• **Steatosis <5%**	**9**
• **Steatosis 5- 10%**	**6**
Type of the liver graft:	
• **Right lobe.**	**36**
• **Right posterior sector.**	**4**

Fifteen percent of donors had trifurcated portal vein and seven and half Percent had right anterior portal branch arise from the left portal, Seven donors had a significant segment VIII vein that required reconstruction in the recipient whereas only five donors had a significant accessory inferior right hepatic vein {> 5 mm} that was preserved for re-implantation. The donor operative time was 6.16 ± 0.88 hours with an estimated blood loss 1118 ± 833 ml. Blood transfusion in 14 donors with 2.67 ± 2.03 units and fresh frozen plasma in 15 donors with 2.7 ± 1.38 units. ICU length of stay for all donors was 2 ± 1 days and hospital length of stay for all donors was 9 ± 3days.

Table 2 Donors' operative data

	Min	max	mean	SD
Length of operation (hour)	4	8	6.16	± 0.88
Blood loss (ml)	300	4500	1118	± 833
Blood transfusion (unit)	1	8	2.67	± 2.03
FFP transfusion (unit)	1	11	2.7	± 1.38
Hospital length of stay (day)	7	22	9.3	± 3.32

Table 3 Donor liver graft characteristics

	mini	max	Mean ± SD
CT total liver volume " cm3" for right lobe graft	1239	2200	1677± 225.3
CT total liver volume " cm3" for right posterior sector graft	1451.6	1841.73	1653.6±187.1
CT right lobe liver volume "cm^3"	650	1360	957.8±177.1
Actual right lobe graft weight " gm "	510	1166	858.9±165.3
Donors of RT lobe graft remained volume "%"	37.1	60	47.1±5.2
Actual right posterior sector graft weight " gm '	510	726	597±104.8
Donors of RT posterior sector graft remained volume "%"	59.46	70.14	63.7±4.8

Surgical morbidity rate was 47.5% {19 cases} and is shown in table 4. No donor operation was aborted and no donor deaths occurred. 52.5% {21 donors "} had no complications. The majority of the observed complications were minor and self limited. No morbidity in the four donors of right posterior sector graft, all donors' morbidity occurs in right lobe graft donors Five donors developed right sided pleural effusion; one of them was symptomatic and required thoracocentesis. Four patients developed small postoperative bile collection, one of them required only US guided aspiration and the others required application of US guided pigtail catheter drainage; one of them was presented of persistent bile leak after the pig tail that required ERCP and biliary stent.

Reoperation was necessary in three donors {7.5%} for postoperative bleeding, evacuation of postoperative hematoma and removal of stitches sinus, respectively. Postoperative bleeding was most likely the result of slipped ligature of stump of portal vein that required clamping with vascular clamp and re-

closure. The second patient requiring reoperation developed anemia on postoperative day 3 and was found to have hematoma at the site of the right hepatic lobe. The patient's HB. conc. was 6.2 mg/dl}, two units of packed RBCs were given to him, but at the fifth day patient complained of fever, abdominal pain and hiccough, CT revealed huge hematoma related to the cut surface at the site of right lobe of the liver, evacuation of the hematoma and wash of the abdomen with saline was done then closure of the abdomen with two tube drains.

Table 4. Donor morbidity

Complication	Number of patient
Biloma biliary leak	4{ 3 US pigtail drainage} 2{ one ; ERCP}
Postoperative bleeding	1{reoperation}
Postoperative hematoma	3{1; reoperation}
Postoperative fluid collection	2{ US aspiration}
Pneumonia	2
cholangitis	2
Wound problem	5"3 seroma , 1 infection , 1 stitche sinus {reoperation}
Transient ascites	4
Scrotal edema	1
Pleural effusion	5{ 1; thoracocentesis}
Paralytic ileus	2
HAV infection	2

Liver regeneration and function recovery:

Liver regeneration was measured at 1week and at 1, 3, 6 months postoperatively and calculated using helical CT scan. The four donors of the right posterior graft nearly reach the preoperative whole liver volume after 3months. Two donors of right lobe graft "one male, one female" also, nearly reached the preoperative whole liver volume after 6 months. Postoperative liver enzymes revealed initial high elevation in the first 3 days then decline gradually, reached the baseline at postoperative day # 30. The T.bilrubin returned to normal level at postoperative day 7. Duplex US was done at first two days to exclude any portal vein thrombosis and fluid collection and then at the time of CT volumetry. The liver duplex revealed increased in the portal flow and to some extent increased portal pressure leading to transient splenomegaly for 3 months then return to normal size afterwards.

- **Liver graft regeneration according to the type of the graft:**

Donor residual liver volume was 63.7 $\pm$ 4.8 % of RT post. Sector reached to 99.6 $\pm$ 0.21% at POD # 90, and was 47.1 $\pm$ 5.4% of RL donors reached to 95.2 $\pm$ 1.7% at POD #180. The increased ratios of the remnant liver were high in the RL donors when compared with the RT Post. Sector donors {P<0.001}. However, the liver enzymes and total bilirubin levels were high in the RL donors in the 1st week.

Table 5. Liver graft regeneration according to the type of the graft.

days	Type of the graft	Remained liver vol."cm^3"	% of the original liver vol.	% of regeneration per day from previous visit	Increased ratio of remnant vol.	P value
0	RT post. Sector : 4	1047 ±130.2	63.7 ± 4.8			
	RT lobe : 36	793.7 ± 146.7	47.1 + 5.4			
7	RT post. Sector : 4	1431.9 ± 115	86.7 ± 1.6	3.28 ± 0.23	37.4 ± 11.3	<0.001
	RT lobe : 36	1170.8 ± 169.4	69.8 + 5.1	3.24 + 0.73	49.5 + 12	<0.001
30	RT post. Sector : 4	1582 ± 129.9	95.1 ± 1	0.36 ± 0.044	51.1± 12	<0.001
	RT lobe : 36	1360.3 ± 186.7	80.6 + 1.9	0.47 + 0.08	71.4 + 23.5	<0.001
90	RT post. Sector : 4	1647 ± 148.9	99.6 ± 0.21	0.075 ± 0.003	57.3 ± 14.2	<0.001
	RT lobe : 36	1488.1 ± 202	88.5 + 2	0.13 + 0.03	87.5 + 25.4	<0.001
180	RT lobe : 36	1599.8 ± 214	95.2 ± 1.7	0.075 + 0.019	101.6 ± 26.9	<0.001

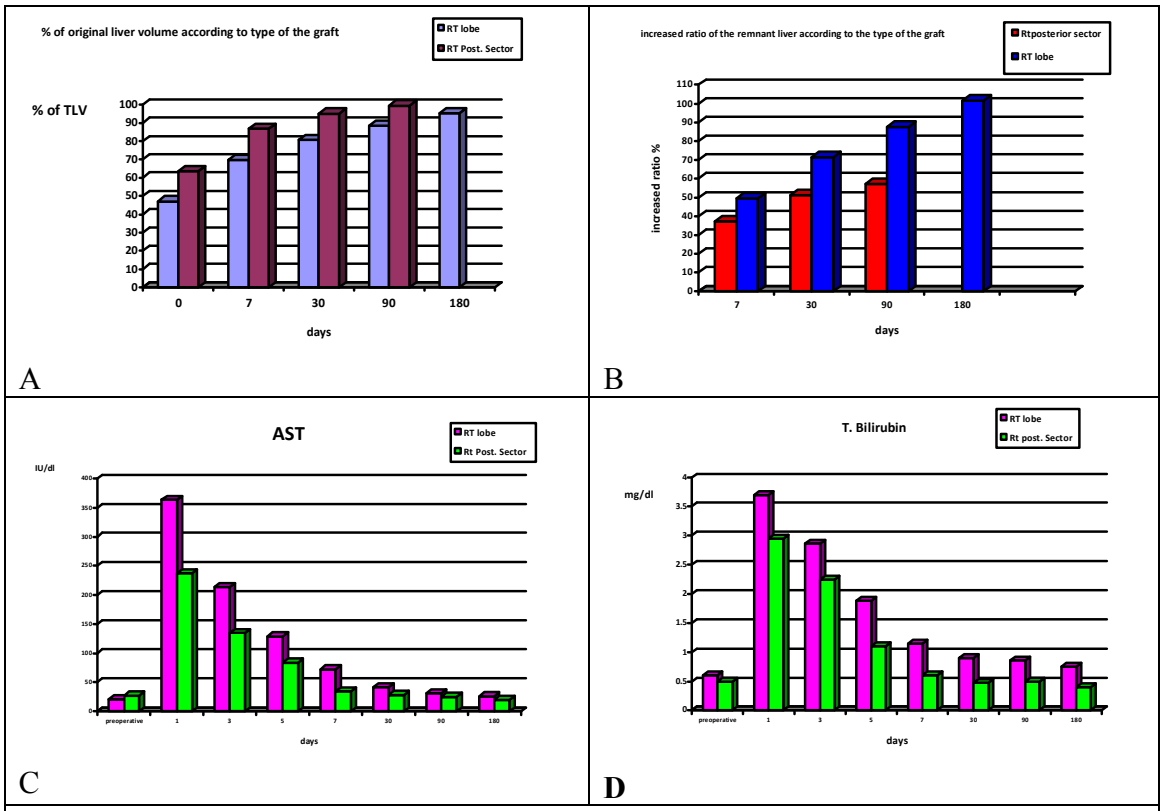


Fig. 2: postoperative liver regeneration and function recovery according to the type of the graft.
A: % of TLV, B: increased ratio of the remnant liver volume, C: AST , D: T.Bilirubin.

- **Liver regeneration according to donor sex:**

Right hepatectomy was carried in 7 female donors and 29 male donors. Donor residual liver volume was 47.9 ± 5.3 % in male donors reached to 95.3 ± 1.8 % at POD #180, and was 43.6 ± 4.7% in female donors reached to 94.6 ± 1.1% at POD #180. The remnant liver of female group show rapid regeneration than male group especially in POD#7, increased ratios were 68.8% in females vs. 44.2% in males and remnant liver in female group increased from 43.6% to 74.3% of TLV vs. from 47.9% to 68.7% of TLV in male group, "% of regeneration per day" was 4.39% in female group vs. 2.97% in male group in POD #7 {P<0.001}.

- **Liver regeneration according to donor age:**

All RL donors were analyzed. There were two donors in 10's, twenty one donors in 20's, and thirteen donors in 30's of donor age**.** The preoperative TLV, remnant liver volume showed no significant difference between age groups. The liver regeneration was slow in the teenagers at POD #7, the increased ratio was33.9% in group1, 46.9% in group 2 and 53.9% in group 3 (P<0.001). Then, there were no significant differences between the 3 groups.

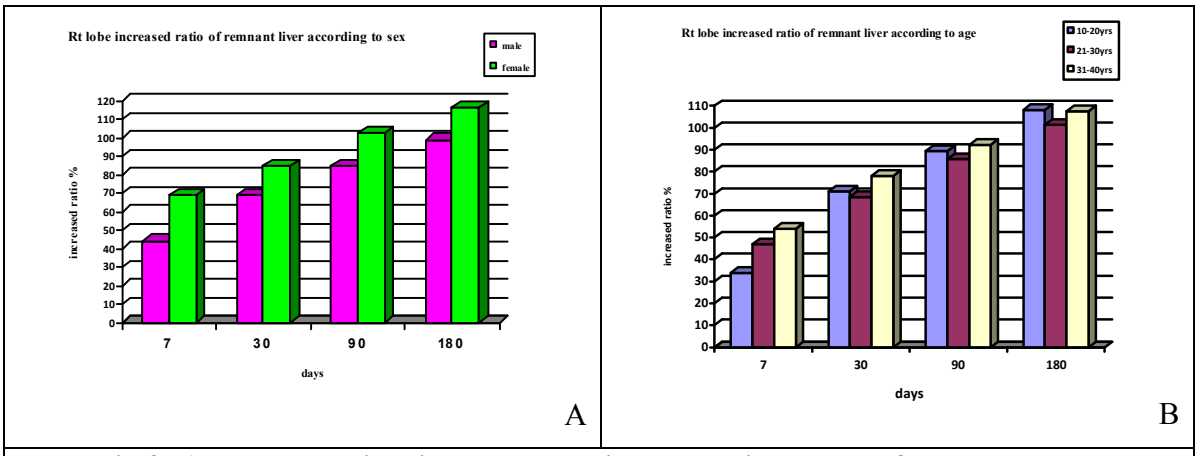


Fig.2: A: postoperative liver regeneration according to sex of the donor, B: postoperative liver regeneration according to age of the donor.

- **Liver regeneration according to size of remnant liver:**

We divided all donors to group with remained liver volume less than 40% of preoperative TLV (group 1, N=2), between 40% and 50% (group 2, N=23) and more than 50% (group 3, N=15).The remnant liver volume was 69.1% of TLV increased to 94.1% of TLV in group 1, 69.1% of TLV increased to 95.1% of TLV in group 2 and 69.5% of TLV increased to 94.6% of TLV in group 3. The increased ratios were high in group 1(P<0.001).

- **Liver regeneration according to remained liver/donor weight (RL/DW) ratio:**

We divided all donors to groups according to RL/DW ratio to group 1 " between 0.6 and 0.8 (N=9), group 2 "between 0.81 and 1 (N=15) and group 3 "between 1.01 and 1.2 (N=16).The remnant liver volume was 41.2 % of TLV increased to 95.8 % of TLV in group 1, 47.7 % of TLV increased to 95 % of TLV in group 2 and 54.3 % of TLV increased to 95.1 % of TLV in group 3. The increased ratios were high in group 1(P<0.001).

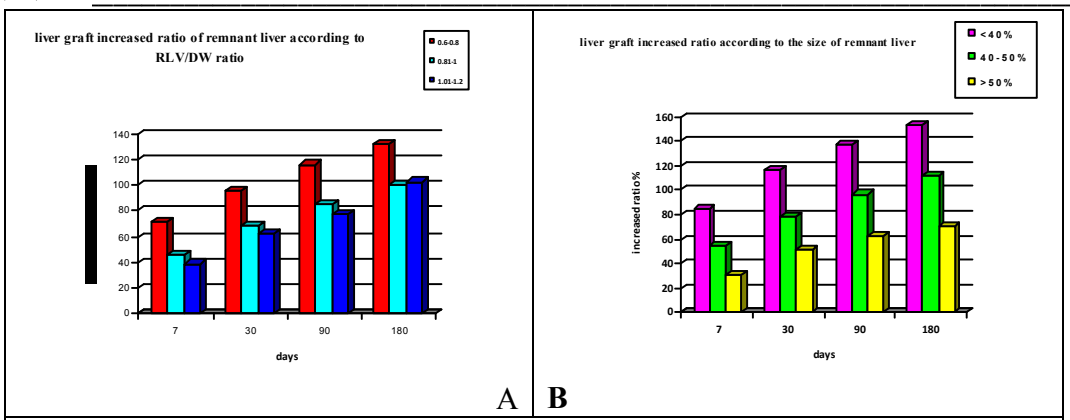


Fig. 3: A: postoperative liver regeneration according to RL/DW ratio, B: postoperative liver regeneration according to size of the remnant liver.

- **Liver regeneration; according to fatty change of donor liver:**

All donors were divided into 3 groups, such as no fatty degeneration group 1(no steatosis) in 25 donors, group 2 with fatty change less than 5% in 9 donors and group3 with fatty change between 5 and 10% in 6 donors. There was no significant difference between groups on regenerated liver volume "Reg.LV" and serial AST, ALT, and T.bil. levels.

- **Liver regeneration according to postoperative complication and blood transfusion:**

We divided the RL donors according to blood transfusion into 2 groups, no blood transfusion in group1 in 22 donors and with blood transfusion in group2 in 14 donors and we divided also the donors according to postoperative complications into group {morbidity} in 19 donors and group 2 {no morbidity} in 17 donors .There was no significant difference between groups on regenerated liver volume "Reg.LV" and serial AST, ALT, and T.bil. levels.

DISCUSSION

Liver transplantation is a recent solution for patients with end stage liver disease. Graft of the right lobe of the liver was world wild trend for living donor liver transplantation because of enough volume and function of right lobe to meet the metabolic need of adult recipient.[7] The development of refinements in surgical techniques, unique anatomy and physiology of the liver expands living donor partial liver transplantation.[10]

The reported morbidity rate associated with donor right hepatectomy has varied greatly [5, 13]. In our study, all unexpected and untoward events were recorded. We had observed that no mortality happened in our donors and all morbidity that happened to the donors did not affect the liver regeneration of the remnant liver. The reported morbidity rate was 47.5% that had been occurred in 19 right hepatectomy donors. Most of these adverse events were minor and self limited; however ten patients required invasive procedures including surgery.

Multi-slice CTA was used for evaluating liver vascular anatomy; CT is also a useful technique for estimating right-lobe graft volume and right posterior sector graft volume. During the performance of CT volumetry the line of demarcation between the right and left lobe was 1cm on the surface of the liver 1cm to the right of the

middle hepatic vein that is safest for the donor as not harvest the MHV.[9, 11]

The human body responds to partial hepatectomy not by regenerating lost segments but by inducing hyperplasia in the liver remnant. [15] Normal livers also begin to regenerate within 3 days and have reached its original size by 6 months.[14]

The process of restoration of liver volume in humans is initiated by the replication of various types of intrahepatic cells, followed by an increase in cell size. The onset and peak of hepatocyte replication vary among species.[17] In humans, replication of hepatocytes generally starts within 1 day after a major resection.[12] The initiation and synchronization of replication in different types of hepatic cells depend on the extent of the resection, tissue damage, or both. Low-grade tissue damage or a relatively small resection (removal of less than 30% of the liver) substantially reduces the replication rate, which also appears to be less synchronized than after a large resection (removal of 70% of the liver). [16]

In this study the regeneration of the remnant liver was significantly different with sex of the donors, age of the donors, type of the graft, size of the remnant liver and the remnant liver / donor weight ratio, and there was no effect of steatosis of the graft, anatomical vascular and biliary variations, BMI, operative time, estimated blood loss, postoperative complications, or perioperative liver function tests on liver regeneration. Our result showed also that posterior sector graft was safe to the donor especially when it was sufficient to the recipient.

In our study, we had thirty six right lobe graft donors and four right posterior sector graft donors, in all donors with right lobe graft, preservation of the MHV had to be done to prevent congestion of segment IV and maintain the regeneration of segment IV. The remnant liver regenerated was more in right lobe graft donors than in right posterior graft donors; the overall liver regeneration was 95.2 % of total liver volume by 6 months in donors of right lobe graft and nearly reached the total liver volume in donors of right posterior sector graft by 3 month. All the forty donors achieved normal liver enzymes within 1 month postoperative and achieved normal total bilirubin within one week.

The volume of the right lobe was bigger in female donors than male donors; we harvested 56.4% of TLV in female donors and 52.1% of TLV in male donors that means the remnant liver size in female was less than in males. The remnant liver of female group show rapid regeneration than male group especially in POD#7, we found this to be curious, knowing that estrogen induces liver regeneration.

The remnant liver of teenagers group showed significant slow regeneration until POD #7, we couldn't explain the reason of this result .The liver regeneration of this group had no difference to other group in POD#30, POD#90 and POD#180.

Remnant liver also regenerated more rapidly and persisted significantly until POD#180 in the donors who had a remnant liver volume less than 40% of TLV. And in donors who had remained liver / donor weight ratio from 0.6 to 0.8. Our result showed more rapid regeneration of liver in those who had a small remnant liver volume especially early after resection, and the remnant liver volume of 35% of TLV will be enough to safe recovery of liver function.

Because the portal venous flow velocity has a trigger effect on liver regeneration. [18] The increased portal flow in the donors who got a less a mount of remnant liver and donors who had less remained liver / donor weight ratio might influence more rapid liver regeneration. We check portal flow

increased velocity and volume by duplex US liver at the time interval of CT volumetry.

Because of the risk of primary non-function of graft, we did not use steatotic liver as donor. [7] In our program we don't use donors with fatty liver more than 10% of steatosis. As a result, we could not find any differences of liver regeneration and function recovery between the donors group with different degree of steatosis.

In conclusion, the donor liver regenerated up to 95.3% of preoperative volume at 6 months postoperative with full recovery of liver function at POD #30.Right lobe donors suffered more complications and need more meticulous operative and postoperative care than right posterior sector graft donors.

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