Surgical Stress Hyperglycemia Associated With New-Onset Diabetes in Living Kidney Donors

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ABSTRACT

Background. The aim of this study is to investigate the frequency and risk factors of new-onset diabetes after donation in kidney donors without diabetes.

Methods. Living donors of kidney transplants between 1998 and 2016 were evaluated. To detect the blood glucose profile of the donors, preoperative fasting glucose (pro-G), nephrectomy evening glucose (nG), and postoperative day 1 fasting glucose (post-G) values were measured.

Results. A total of 195 cases were included in the study. The mean follow-up time in months ± SD (range) was 56 ± 45 (12–215). Of these, 28 (14.3%) donors developed diabetes. The pro-G (103 ± 7.6 vs 93 ± 9.0), nG (208 ± 122 vs 163 ± 67) and post-G (121 ± 25 vs 111 ± 21) values of the donors with new-onset diabetes were higher. Nineteen donors (9.7%) had normal pro-G, nG, and post-G values (group A). However, there were 153 (78.5%) cases with at least 1 abnormal value (group B) and 25 (12.8%) cases that had abnormal values in all (pro-G, nG, and post-G) measurements (group C). The incidence of new-onset diabetes was 0 (0%) in group A, 11% in group B, and 48% in group C ($P < .001$). In multiple regression analysis, pro-G (Exp[B], 1.08; 95% CI, 1.04–1.13; $P < .001$) and basal glomerular filtration rate (Exp[B], 0.96; 95% CI, 0.94–0.99; $P < .01$) independently associated with new-onset diabetes.

Conclusions. In kidney donors without a history of diabetes, the development of diabetes after donor nephrectomy is an important problem. Pre- and postoperative blood glucose levels provide important information to predict these cases.

DIABETES mellitus (DM) is an endemic problem both in Turkey and in the world. In the general population, the risk of diabetes is increasing, and this risk may be increased in live donors without a previous history of diabetes after undergoing donor nephrectomy. Furthermore, basal and stress glucose profiles may provide important information about new-onset diabetes after donation. Recent studies have investigated the risk of developing diabetes after acute and critical illness [1,2]. In many of these cases, stress hyperglycemia poses a risk for both a poor outcome and new-onset diabetes [2–4]. In a systematic review, 28% of the patients with severe hyperglycemia at admission were reported to develop diabetes after discharge [2].

In live donors without a diabetic history, the risk of end-stage renal disease (ESRD) after nephrectomy is increasing and new-onset diabetes is of importance in etiology of ESRD. In this study, the frequency and risk factors of diabetes after donation in living kidney donors were investigated.

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METHODS

Living donors of kidney transplants between January 1998 to December 2016 were evaluated. Eligible donors were those with age >18 years, glomerular filtration rate (GFR) >70 mL/min/1.72m^2, body mass index (BMI) ≤35.0 kg/m^2, and proteinuria <300.0 mg/d. Subjects with a history of diabetes and <1 year of follow-up were excluded from the study. Donors with a history of hypertension but without end-organ vascular damage and who had normal ambulatory blood pressure measurement with a single drug treatment were included in the study. Baseline and follow-up data of donors were obtained retrospectively from files. The diagnosis of new-onset DM depended on the presence of any of the following: fasting blood glucose ≥126.0 mg/dL, random blood glucose ≥200.0 mg/dL, diabetes symptoms, oral glucose tolerance test 2-hour plasma glucose ≥200.0 mg/dL, or glycated hemoglobin A_{1c} ≥6.5%.

In all patients, preoperative fasting glucose (pro-G), glucose on the evening of nephrectomy (nG), and postoperative day 1 fasting glucose (post-G) values were measured and recorded. Normal values for pro-G and post-G were (<100.0 mg/dL) and a normal value for nG was (<140.0 mg/dL). According to this triple glucose profile scheme, patients were evaluated in 3 subgroups. Patients in group A had normal pro-G, nG, and post-G values; those in group B had at least 1 abnormal value; and those in group C had abnormal values in all (pro-G, nG, and post-G) measurements.

STATISTICAL ANALYSIS

All analyses were performed with SPSS version 15.0 (IBM, Armonk, New York, United States) for Windows statistical package. The mean and SD of all values were calculated. Mean values of the 2 groups were compared using the Student *t* test or a nonparametric test if the data was not normally distributed. DM development rates of the groups with both low and high preoperative fasting glucose groups and groups A, B, and C were compared using the Kaplan-Meier analysis. $P < .05$ was considered to be statistically significant.

RESULT

Included in the study were 195 cases. The mean follow-up in months ± SD (range) was 56 ± 45 (12–215). The mean age in years ± SD (range) was 47 ± 11 (19–82) and 49% of donors were women. Of the cases, the average pro-G, nG, and post-G were 94.2 ± 9.6 (57–122), 169 ± 79 (85–631), and 113 ± 21 (66–240) mg/dL, respectively. In the follow-up, 28 (14.3%) donors developed diabetes. The pro-G (103 ± 7.6 vs 93 ± 9.0; $P < .001$), nG (208 ± 122 vs 163 ± 67; $P = .06$), and post-G (121 ± 25 vs 111 ± 21; $P = .02$) values of the donors with new-onset diabetes were higher. Donors who developed diabetes had lower basal GFR values and higher systolic and diastolic blood pressure ($P < .05$). In these cases, the final outpatient control kidney function was equivalent to the donors without diabetes, but the frequency of hypertension was higher ($P < .05$) (Table 1). When donors with pro-G <100.0 mg/dL (n = 152) were compared with those having preoperatively impaired fasting glucose (IFG) (n = 43, pro-G >100.0 mg/

Table 1. The Comparison of Patients With and Without Diabetes Mellitus

	All Cases (n = 195)	With DM (n = 28, 14.3%)	Without DM (n = 167, 85.7%)	*P* Value
Age (y), mean ± SD	47 ± 10	50 ± 11	47 ± 11	.19
Sex (F/M) (%)	51	46.4	52	.58
Body mass index (kg/m^2), mean ± SD	26.8 ± 3.9	27.4 ± 4.1	26.7 ± 3.9	.35
Obesity (%)	23	29	22	.41
Hypertension (%)	3	11	2	.15
SBP (mm Hg), mean ± SD	118 ± 13	124 ± 13	117 ± 13	.02*
DBP (mm Hg), mean ± SD	76 ± 9.4	81 ± 9.4	76 ± 9.3	<.01*
Pro-G (mg/dL), mean ± SD	94.2 ± 9.6	103 ± 7.6	93 ± 9.0	<.001*
nG (mg/dL), mean ± SD	169 ± 79	208 ± 122	163 ± 67	.06*
Post-G (mg/dL), mean ± SD	113 ± 21	121 ± 25	111 ± 21	.02*
HbA_{1c} (n = 70), mean ± SD	5.53 ± 0.39	5.67 ± 0.45	5.49 ± 0.36	.12
Baseline serum urea (mg/dL), mean ± SD	29 ± 8.6	31 ± 8.9	29 ± 8.6	.26
Baseline GFH (mL/min/1.73 m^2), mean ± SD	103 ± 22	95 ± 21	104 ± 21	.03*
Baseline serum uric acid (mg/dL), mean ± SD	4.6 ± 1.3	5.0 ± 1.5	4.5 ± 1.3	.18
Baseline proteinuria (mg/day), mean ± SD	123 ± 67	129 ± 64	122 ± 68	.61
Baseline TG (mg/dL), mean ± SD	145 ± 88	172 ± 116	141 ± 82	.07
Baseline HDL (mg/dL), mean ± SD	47 ± 12	46 ± 10	47 ± 12	.58
LC body mass index (kg/m^2), mean ± SD	27.7 ± 4.3	28.3 ± 4.1	27.6 ± 4.3	.44
LC obesity (%)	31	32.1	35	.72
LC FBG (mg/dL), mean ± SD	97 ± 13	107 ± 23	95 ± 9.7	.01*
LC serum urea (mg/dL), mean ± SD	34 ± 8.9	37 ± 11	33 ± 8.4	.04*
LC GFR (mL/min/1.73 m^2), mean ± SD	69 ± 17	67 ± 16	70 ± 17	.40
LC. HT cases (%)	12	36	8	<.01*

Abbreviations: DBP, diastolic blood pressure; DM, diabetes mellitus; F, female; FBG, fasting blood glucose; GFR, glomerular filtration rate; HbA_{1c}, glycated hemoglobin A_{1c}; HDL, high-density lipoprotein cholesterol; HT, hypertension; M, male; LC, last control; nG, nephrectomy evening glucose; post-G, postoperative first day glucose; pro-G, preoperative fasting glucose; SBP, systolic blood pressure; TG, triglyceride.

*Denotes a statistically significant value.

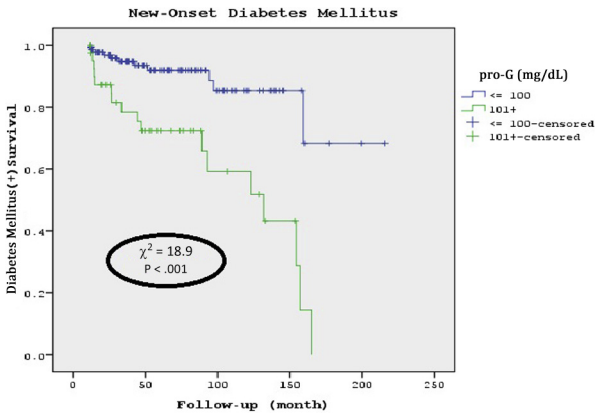

Fig 1. The comparison of diabetes mellitus development rates of the group with low and high preoperative fasting glucose (pro-G) in the Kaplan-Meier analysis.

dL); donors with IFG were older (51 ± 10 vs 46 ± 11; $P < .05$), had lower baseline GFR (97 ± 19 vs 104 ± 22; $P < .05$) and higher incidence of DM (40% vs 7%; $P < .001$) (Fig 1).

In 100 patients (51.2%), nG was >140.0 mg/dL and in 145 cases (74.3%) post-G was >100.0 mg/dL. The incidence of postnephrectomy diabetes in donors with normal and impaired nG and post-G were 18% vs 10.5% ($P = .15$) and 18% vs 4% ($P = .01$), respectively.

Nineteen donors (9.7%) had normal pro-G, nG, and post-G values (group A). However, there were 153 (78.5%) cases with at least 1 abnormal value (group B) and 25 (12.8%) cases having abnormal values in all (pro-G, nG, and post-G) measurements (group C). The incidence of postnephrectomy diabetes in group A was zero (0%) while it was 11% in group B and 48% in group C ($P < .001$) (Fig 2). In multiple regression analysis including variables as age,

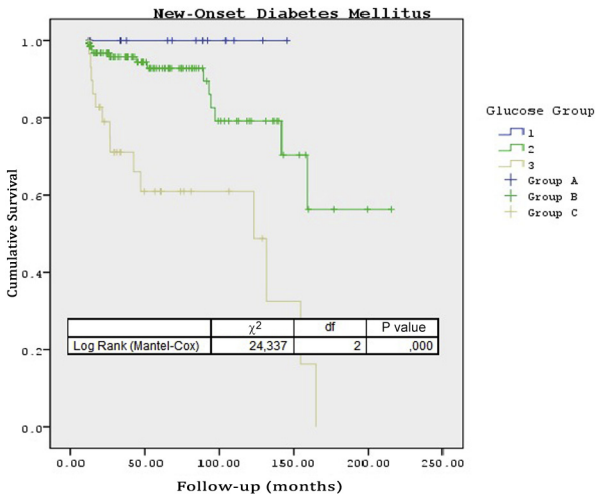

Fig 2. The comparison of diabetes mellitus development rates of the groups among A, B, and C in the Kaplan-Meier analysis.

diastolic blood pressure, GFR, pro-G, nG, and post-G, pro-G (Exp[B], 1.08; 95% CI, 1.04–1.13; $P < .001$) and basal GFR (Exp[B], 0.96; 95% CI, 0.94–0.99; $P < .01$) independently predicted diabetes development.

DISCUSSION

In this study, we aimed to investigate the biochemical and demographic factors in predicting the development of diabetes after nephrectomy in live kidney donors. We found that pro-G and measured GFR levels were significantly associated with the development of diabetes after nephrectomy. Forty percent of donors with IFG before operation (n = 43, pro-G >100.0 mg/dL) developed DM after nephrectomy. These donors were also older and had had lower predonation GFR values. In support of our findings, 143 live kidney donors with IFG before donation were compared with donors with normal fasting glucose, and postdonation diabetes developed in 16% and 2.2% of the cases, respectively [5].

Almost 10% of the cases in our series had a normal blood glucose profile and none of them had developed postdonation diabetes. On the contrary, about half of the cases with abnormal values in all measurements developed new-onset diabetes. Different mechanisms may be responsible for this situation. Essentially, the basal metabolic status in our patients may be prone to diabetes because their pro-G values were relatively higher. Secondly, acute and critical stress (eg, infection, surgery, etc) induced hypermetabolism, inflammation, and counter-regulatory hormone levels that may impair carbohydrate metabolism, increase peripheral insulin resistance, and decrease insulin secretion [1,2]. This often causes transient stress hyperglycemia. However, several authors have suggested that stress hyperglycemia could proceed after hospital discharge. This is thought to relate to glycemic memory [2]. In half of our cases, the nG value was >140.0 mg/dL, and in a quarter of the cases it was >200.0 mg/dL. Finally, the risk of diabetes is increasing in the solitary kidney population [6,7]. Pathogenesis of new-onset diabetes after live kidney donation needs to be investigated in longitudinal prospective studies. Considering poor glucose profile and glycemic memory, a dramatic increase in the risk of diabetes may be expected in this population.

Diabetes is an endemic problem both in our country and in the world. Even in the general population, the risk of diabetes is increasing, and this risk may be increased in the solitary kidney population due to hormonal and metabolic changes along with GFR change [6,7]. In these cases, concomitant hypertension may adversely affect renal survival. In a large-scale study that included 4030 living kidney donors, nearly 1% developed ESRD after nephrectomy. In almost 50% of this group, the etiology of the ESRD was found to be DM or hypertension [7]. In another study, variables such as age, sex, BMI, fasting blood glucose, year of donation, estimated GFR, blood pressure, smoking, and relationship to the recipient were

analyzed to predict their effect on the development of DM after donation. Solely, BMI and fasting blood glucose level significantly predicted postdonation DM in these 4000 living kidney donors [6]. In a study conducted on 4650 kidney donors consisting essentially of white individuals (70%), the estimated risk of developing diabetes in the 5 years after donation was 4%. The relative frequency of diabetes increased 5% for each year of age at the time of donation [8]. Similarly, in a study conducted in Eastern society, diabetes developed in 6.8% of the cases above 10 years after donation, and all of them had significant weight gain after donation [9]. In another study that included 41,000 living kidney donors, the frequency of diabetes development at 6 months, 1 year, and 2 years after donation was found to be 2, 6, and 15 for every 10,000 donors. These findings reaffirm that new-onset DM after donation is rare. But, every 10-year increment of older age and every 5-unit increase of BMI in living kidney donors is reflected by a 50% increased relative risk of developing DM in this large series [10].

The relative risk of DM-induced ESRD in kidney donors is as high as 7.7 after at least 2 decades of donation when compared with the time frame of $\leq$10 years of donation [11]. For this reason, especially in the selection of young live donors, it is necessary to determine the parameters predicting the development of postdonation diabetes with high accuracy in the preoperative period.

CONCLUSIONS

As a result, in kidney donors without a history of DM, the development of diabetes after donor nephrectomy is an important problem. Long-term monitoring of donors is not practical. Indeed, in the majority of retrospective donor evaluations, the rate of patients without follow-up is very high. For this reason, it is necessary to accurately identify the parameters that predict diabetes prior to kidney donation. In this context, pre- and postoperative blood glucose levels may provide important information.

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