Study of the Risk Factors and Complications of Diabetes Mellitus After Live Kidney Donation

Mohammed M. Abuelmagd,[1] Ayman M. Nagib,[1] Megahed M. Abuelmagd,[2] Ayman F. Refaie,[1] Yasser A. Elhindi,[3] Mohammed F. Ahmed,[3] Mohammed H. Ali,[3] Hanzada M. Elmaghrabi,[1] Mohammed A. Bakr[1]

Abstract

Objectives: **Kidney donors, similar to the general population, are at risk for development of type 2 diabetes mellitus. The course of donors who develop type 2 diabetes mellitus has not been well studied. This work is aimed at estimating the incidence of diabetes after kidney donation, and study some risk factors and some complications of diabetes mellitus after donation.**

Materials and Methods: **The material of this record based work comprised the records 2267 donors who donated 1 of their kidneys between 1976 and 2014 in the Urology and Nephrology Center, Mansoura University, Egypt, and regularly followed-up at its outpatient clinic. There were 388 donors included in the study and their medical records were revised.**

Results: **Postdonation weight gain and family history of diabetes mellitus were statistically significant on both the development of diabetes mellitus, high, very high albuminuria, and/or decreased creatinine clearance. Metformin and insulin use seemed to significantly reduce the protein excretion, and creatinine clearance decline in the studied group.**

Conclusions: **There is a significant effect of the family history of diabetes mellitus on the development of high, very high albuminuria, and/or decreased creatinine clearance.**

From the [1]Mansoura Urology and Nephrology Center; [2]Mansoura Internal Medicine Specialized Hospital; and the [3]Zagazig University Department of Internal Medicine, Egypt

Acknowledgements: *The authors declare that they have no sources of funding for this study, and they have no conflicts of interest to declare.*

Corresponding author: *Mohammed Megahed Mohammed Abu Elmagd, Galaa Street Aya Tower, Mansoura, Al Daqahliah, Egypt*
Tel: *+20 205 0235 1736* ***E-mail:*** *mg26984@gmail.com*

Experimental and Clinical Transplantation (2015) Suppl 1: 111-116

Key words: *Family history of diabetes mellitus, Postdonation albuminuria, Donor exclusion criteria, Postdonation diabetes mellitus, Postdonation obesity*

Introduction

Living kidney donation has become an essential part of transplant practice. Historically, this has been attributed to the shortage of deceased donor kidneys and the growing waiting list of potential recipients. However, kidney transplant from a living donor has become the treatment of choice for many patients and their families, offering optimum patient and graft survival.[1]

Studies over the last 60 years have provided considerable evidence regarding the ability of the kidneys to make and release glucose under various physiologic conditions. Yet traditionally, the kidneys have not been considered an important source of glucose (except during acidosis or after prolonged fasting), with most clinical discussions on glucose dysregulation centering on the intestine, pancreas, liver, adipose tissue, and muscle.[2] However, the significance of the kidneys' contribution to glucose homeostasis, under both physiologic and pathologic conditions, has become well-recognized, and is thought to involve functions beyond glucose uptake and release. Besides the liver, the kidney is the only organ capable of generating sufficient glucose (gluconeogenesis) to release into the circulation, and it is also responsible for filtration and subsequent reabsorption or excretion of glucose.[3] These findings have provided considerable insight into the myriad of pathophysiologic mechanisms involved in the development of hyperglycemia and type 2 diabetes mellitus (T2DM).[4]

DOI: 10.6002/ect.mesot2014.O60

Diabetes mellitus is an absolute contraindication to living donation. Prospective donors with an increased risk of T2DM because of family history, ethnicity, or obesity should undergo a glucose tolerance test and the only considered as donors if this is normal.[5] Yet it is unknown whether developing T2DM after donating a kidney leads to a higher risk of experiencing acceleration in glomerular filtration rate (GFR) decay when compared to nondiabetic donors or diabetics with 2 kidneys.[6] Some transplant centers decline kidney donors with a strong family histories of T2DM because of theoretical concerns regarding the possible additive effect of hyperfiltration that is instigated by diabetes and reduction in renal mass.[7]

Materials and Methods

Subjects

Subjects of this record-based work comprised the records 2267 donors who donated their kidneys between 1976 and 2014 at the Urology and Nephrology Center, Mansoura University, and regularly followed-up at its outpatient clinic. In this study, we tried to look up donors' paper and/or electronic files. A total of 344 donors were declared dead by a verified hospital patient information system data. A total of 1535 donors did not meet the least frequency of follow-ups required for the inclusion (at least the data of 2 visits per year for the last 3 years until March 2014). After excluding donors who did not fulfill the inclusion criteria, 388 donors were included in this study. The following data were extracted from the donors' files.

Preoperative data

The center policy is to accept living-related donors at the age range between 21 and 60 years, and to include donors with a family history of diabetes mellitus up to the start of this and other corresponding studies Also, the data regarding the preoperative body mass index (BMI) were extracted, donors with BMI ranging between 25 and 30 kg/m^2 were included. However, donors with a BMI between 31 and 40 kg/m^2 were encouraged to lose weight before donation and we did not accept any donor with a BMI > 40 kg/m^2 into the preparation program.

Postoperative data

Serial monitoring of the data regarding donors' BMI, serial monitoring of blood pressure data, identification of the type of antihypertensive treatment if present, serial measurement of fasting blood sugar levels donors with fasting blood glucose between 110 and 126 were considered prediabetics. Also, donors with fasting blood sugar above 126 were considered diabetics and both were considered to have disturbed glucose homeostasis, identification of the type of antihyperglycemic treatment (if present), serial monitoring of postdonation albumin creatinine ratio, serial calculations of the estimated creatinine clearance by the application of the (Chronic Kidney Disease Epidemiology Collaboration) (CKD-EPI) equation,[8] serial monitoring of lipid profile postdonation, and the result of the fundus examinations for the diabetic donors only.

Statistical analyses

Statistical analyses were performed with SPSS software (SPSS: An IBM Company, version 16.0, IBM Corporation, Armonk, NY, USA). The data was analyzed using the *t* test for comparison of continuous data, and the chi-square test for comparison of simple proportions. *P* value less than .05 were considered statistically significant.

Results

Among the 388 studied donors 43 became diabetic at a mean interval of 6.9 ± 5.8 years postdonation. Among them there were 19 men and 24 women. Their mean age was 48.39 ± 7.66 years at the time of diagnosis of Diabetes mellitus (DM) and they were significantly ($P < .0001$) older than the studied 345 nondiabetic donors at the time of the initiation of this study. The mean average BMI at their serial follow-ups was significantly ($P = .024$) higher in diabetics when compared to the 345 nondiabetic donors. Among the 43 studied diabetic donors there were 25 donors who developed high albuminuria (albumin to creatinine execretion ratio between 30 to 300 mg/g), high albuminuria (albumin to creatinine execretion ratio above 300 mg/g) and or decreased estimated glomerular filtration rate (eGFR) below 70 mL/min at a mean interval of 10.1 ± 4.6 years postdonation and 6 ± 3.9 years after the diagnosis of DM, among them there were 14 then and 11 women. All of the 25 diabetic donors with high albuminuria, very high albuminuria, and or decreased eGFR below 70 mL/min had varying degrees of diabetic retinopathy (Tables 1, 2, and 3). The highest

frequency of DM was among the > 30 kg/m^2 BMI index group (Table 4). Both frequencies of DM and high albuminuria, very high albuminuria, and or decreased eGFR below 70 mL/min were significantly higher (P = .005, P = .001) among donors with a positive family history of 2 or more family members with DM. The significance was noticeably higher (P = .001) among donors with high albuminuria, very high albuminuria, and or decreased eGFR below 70 mL/min (Table 5).

Among the studied 388 donors there also were 60 donors with prediabetes (impaired fasting glycemia fasting blood sugar between 6.94 and 7.77 mg/dL and or impaired glucose tolerance, 2 hours postprandial between 140 and 199 mg/dL. There was no significant difference between their average BMI and the diabetic group. And their mean age was also not significantly lower than the diabetic group. In comparison, between the studied diabetic versus the prediabetic group, the urinary albumin creatinine ratio was significantly lower (P = .015) in the prediabetic group but the range in this group denoted the presence of microabluminuria also in prediabetic donors. A percentage of 17 (32.6%) of diabetic donors were high albuminuric and 16 (26.7%) of prediabetic donors were high albuminuric. However, 8 of diabetic donors (18.6%) had severely increased albuminuria (very high albuminuria), and only 1 of prediabetics did (1.7%) (Table 6).

In comparison, between diabetic donors with microabluminuria, very high albuminuria, and diabetic donors with normal urinary protein excretion, the BMI index was significantly (P = .04) higher in the very high albuminuric and the high albuminuric groups than the normoalbumiuric group. Also, the mean age was not significantly higher in the very high albuminuric and the high albuminuric groups than the normoalbumiuric group (Table 7). In comparison between diabetic donors on insulin containing regimens versus diabetic donors on other regimens, the estimated clearance was not significantly higher (P = .44) but the urinary albumin creatinine ratio was significantly lower in the insulin group (P = .01). In comparison, between diabetic donors on metformin-containing regimens versus diabetic donors on other (nonmetformin) oral hypoglycemic agents, the estimated clearance was significantly higher (P = .003) and urinary albumin creatinine ratio was significantly lower (P = .04) in the metformin group

Table 1. Demographic and Clinical Characteristics of the Studied 388 Live Kidney Donors

Demographic Characteristics	Value
Donor age at last follow-up M ± SD (y)	50.1 ± 10.5 (27-74)
Donor gender M/F (% Male)	146/242 (37.6%)
Donor age at time of donation M ± SD (y)	41 ± 10.15 (21-61)
Age at diagnosis of DM M ± SD (y)	48.39 ± 7.66 (23-66)
Diabetic donors gender M/F (% Male)	19/24 (39.5%)
Age at diagnosis of high albuminuria, very high albuminuria and or decreased eGFR below 70 mL/min M ± SD (y)	51.19 ± 7.74 (39-68)
Donors with high albuminuria, very high albuminuria and or decreased eGFR below 70 mL/min M/F (% Male)	14/11 (56%)
Interval between donation and development of diabetes M ± SD (y)	6.9 ± 5.8 (1-22)
Interval between donation and development of high albuminuria, very high albuminuria, and or decreased eGFR below 70 mL/min M ± SD (y)	10.1 ± 4.6 (4-21)
Interval between diagnosis of DM and development of high albuminuria, very high albuminuria, and or decreased eGFR below 70 mL/min M ± SD (y)	6 ± 3.9 (1-14)

Abbreviations: eGFR, estimated glomerular filtration rate; DM, diabetes mellitus

Table 2. Frequency and Characteristics of the Studied Diabetic Versus Nondiabetic Donors

Variable	Diabetic Donors (Postdonation)	Nondiabetic Donors	*P* Value
Frequency, (%)	43 (11%)	345 (89%)	< .0001
Predonation BMI M ± SD (y) kg/m^2	29.2 ± 2.3 (22-34)	28.5 ± 3.4 (23-33)	.548
BMI at last follow-up M ± SD (y) kg/m^2	34.1 ± 5.9 (26-52)	31.3 ± 4.1 (23-42)	< .0001

Abbreviations: BMI, body mass index

Table 3. Frequency of the Studied Chronic Complications of Diabetes Mellitus (Diabetic Retinopathy and Nephropathy) Among the Diabetic Group

Chronic Complication	Diabetic Donors Free From the Studied Chronic Complications Frequency, (%)	Diabetic Donors With the Studied Chronic Complications Frequency, (%)	*P* Value
High albuminuria, high albuminuria, and/or decreased eGFR below 70 mL/min	18 (41.8%)	25 (58.1%)	.198
Diabetic retinopathy	11 (25.6%)	32(74.4%)	< .0001

Abbreviations: eGFR, estimated glomerular filtration rate

Table 4. Frequency of Diabetes Mellitus in Different Current Body Mass Index Groups of the Studied Donors

Current BMI group, kg/m^2	Frequency of Diabetes Mellitus Among the Studied Donors (n = 388) Frequency/Total Number of the Groups, (%)
18-25 n = 122	5 (4.1%)
25-30 n = 149	9 (6%)
> 30 n = 117	29 (24.7%)

Abbreviations: BMI, body mass index

Table 5. Frequency of Diabetes Mellitus and High Albuminuria, Very High Albuminuria and/or Decreased Estimated Glomerular Filtration Rate Below 70 mL/min Among Diabetic Donors With a Family History of Diabetes Mellitus Compared With Diabetic Donors With No Family History of Diabetes Mellitus

	Diabetic Donors With A Family History of Diabetes Mellitus Frequency, (%)	Diabetic Donors With No Family History of Diabetes Mellitus Frequency, (%)	*P* Value
DM (n = 43)	28 (64.3%)	15 (35.7%)	.005
High albuminuria, high albuminuria, and/or decreased eGFR below 70 mL/min n = 25	18 (72%)	7 (28%)	.001

Abbreviations: eGFR, estimated glomerular filtration rate; DM, diabetes mellitus

Table 6. Comparison Between the Different Groups of Disturbed Glucose Homeostasis Donors

Variable	Diabetic Donors Postdonation	Donors with Prediabetes	*P* Value
Frequency, (%)	43/388 (11%)	60/388 (15.4%)	< .0001
BMI at last follow-up M ± SD (y), kg/m^2	34.4 ± 4.3 (26-52)	34.2 ± 5.3 (29-51)	.34
Age at time of the study M ± SD (y)	53.9 ± 9.3 (38-74)	51.4 ± 6.54 (37-66)	.134
Creatinine Clearance by CKD-EPI equation M ± SD (y) mL/min/ 1.37m^2	65.8 ± 23 (31-122)	84.6 ± 16.3 (55-126)	< .0001
Urinary albumin creatinine ratio median (range), mg/g	32 (3-6700)	24 (5-350)	.015
Percentage of high albuminuria urinary albumin creatinine ratio between 30-300 mg/g frequency, (%)	17 (32.6%)	16 (26.7%)	.742
Percentage of very high albuminuria (Severely increased albuminuria) urinary albumin creatinine ratio above 300 mg/g frequency, (%)	8 (18.6%)	1 (1.7%)	.0083

Abbreviations: BMI, body mass index; CKD-EPI, chronic kidney disease epidemiology collaboration

Table 7. Comparison Between High Albuminuric and Very High Albuminuric and Normoalbuminuric Diabetic Donors

	High Albuminuric Diabetic Donors	Very high Albuminuric Diabetic Donors	Normoalbuminuric Diabetic Donors	*P* Value
Frequency, (%)	17/43 (32.6 %)	8/43 (18.6%)	18/43 (41.8%)	.07
Average BMI at serial follow-ups M ± SD, kg/m^2	37.8 ± 4.3	39.2 ± 4.8	26.3 ± 6.77	.04

Abbreviations: BMI, body mass index

(Table 8). There was a noticeably significant positive correlation (P = .03 and P < .0001) between the albumin excretion, measured by the urinary albumin creatinine ratio and the BMI of the diabetic whole studied groups of donors (Table 9).

Discussion

Our results disclosed 43 subjects who developed diabetes mellitus after live kidney donation representing a percentage of 11% of the studied 388 donors the percentage which was significantly lower than the percentage of diabetes among general Egyptian population (0.013 y). In Egypt, the percentage of DM was 15.6% according to International Diabetes Federation Atlas 6th Edition 2013.[9] This relatively lower percentage may be explained by the closer follow-ups with earlier identification of the risk factors of diabetes than the general Egyptian population also by the healthy nature of the donor population. The mean BMI of the 43 diabetic donors was 34.3 ± 4.3 kg/m^2, which is higher than the mean BMI of the general Egyptian diabetic population 31.3 kg/m^2, according the IDF Atlas 2013.[9] Also the highest incidence of diabetes was among the BMI group above 30 kg/m^2 being 79.1% of the 43 diabetic donors.

Our study also revealed 60 donors with prediabetes representing a percentage of 15.4% of the studied group (impaired fasting glycaemia and fasting blood glucose between 110 and 125 mg/dL and/or impaired glucose tolerance 2-hour postprandial blood glucose of 140 and 199 mg/dL (according to the WHO Classification of 2007). This

Table 9. Correlation Between BMI and Urinary Albumin Creatinine Ratio of the Studied Donors

	Urinary Albumin Creatinine Ratio mg/g			
	Diabetic Donors Postdonation n = 43		All Studied Group of Donors n = 388	
	r	*P* Value	r	*P* Value
BMI kg/m^2	0.32	.032	0.41	< .0001

Abbreviations: BMI, body mass index

Table 8. Comparison Between Diabetic Donors on Different Antidiabetic Protocols

Variable	Diabetic Donors on Insulin	Diabetic Donors Not on Insulin	*P* Value	Diabetic Donors on Metformin Containing Regimens	Diabetic Donors Other Oral Hypoglycemic Agents	*P* Value
Frequency, creatinine clearance by (%)	14*/43 (32.6%)	29/43 (67.4%)		25/43 (58.1%)	15*/43 (34.8%)	
CKD-EPI equation M ± SD (range), mL/min/1.37 m^2	68.2 ± 16.9 (56-118)	67.2 ± 23 (31-122)	.44	72.2 ± 20.9 (34-122)	55.9 ± 14.6 (31-94)	.003
Urinary albumin creatinine ratio Median (range), mg/g	29 (11-40)	45 (3-6700)	.01	33 (3-1100)	30.5 (11-6700)	.04

Abbreviations: CKD-EPI, chronic kidney disease epidemiology collaboration

*11 donors were on insulin plus (nonmetformin) oral hypoglycemic drugs , 4 donors were on other (nonmetformin) oral hypoglycemic drugs alone, 3 donors only were on insulin alone. No donors were on insulin + metformin.

Figure 1. Correlation Between Body Mass Index and Urinary Albumin Creatinine Ratio of the Diabetic Group

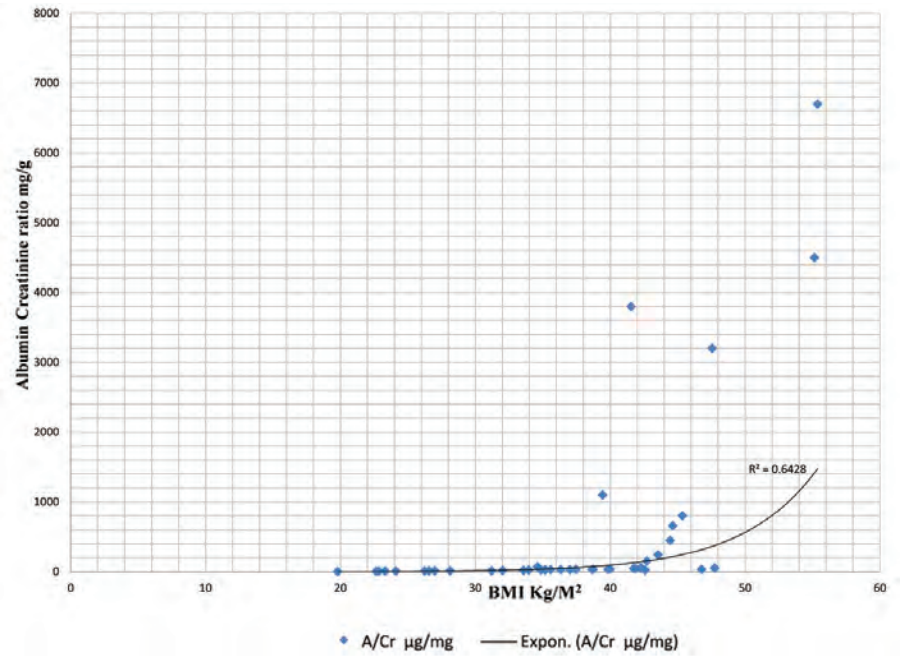


Figure 2. Correlation Between Body Mass Index and Urinary Albumin Creatinine Ratio of the Studied Whole Group of Donors

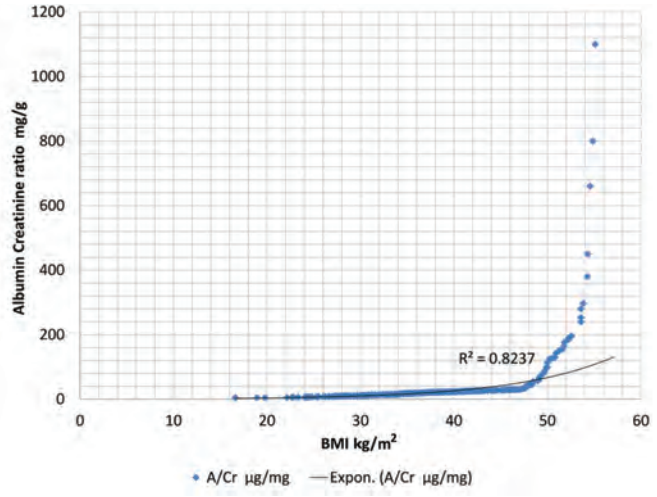
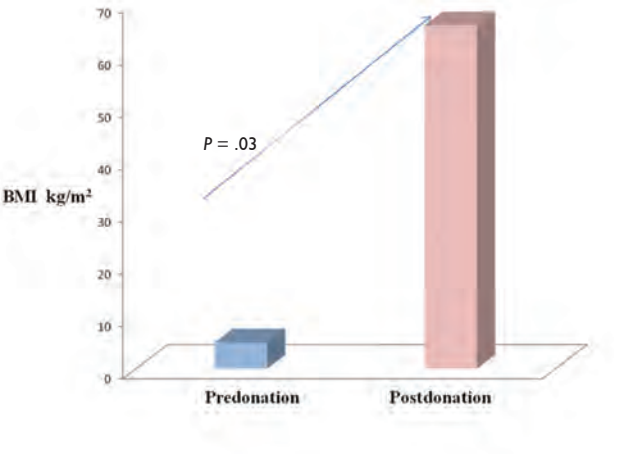


Figure 3. Comparison of the Mean Body Mass Index of the Studied Group at the Day of Donation and the Last Follow-Up Postdonation



percentage is significantly higher ($P < .0001$) than the percentage of prediabetes in the Egyptian general population 6.97% according to IDF Atlas 6th Edition 2013.[9] We also noticed the mean BMI increased significantly ($P = .03$) after donation (Figure 3); this may explain the high frequency of prediabetic status among the studied donors.

Of the studied 43 diabetic donor 58.1% (25 donors) showed high albuminuria, very high albuminuria, and/or decreased creatinine clearance. All those 25 donors had evidence of different types and stages of diabetic retinopathy. The male percentage of them was 56.3%, the mean interval between kidney donation, and development of high albuminuria, very high albuminuria, and/or decreased creatinine clearance was 10.1 ± 4.6 years (range, 4-21 y) and the mean interval between the development of DM and high albuminuria, very high albuminuria, and or decreased eGFR below 70 mL/min was 6 ± 3.9 y (range, 1-14). The percentage of high albuminuria, very high albuminuria, and/or decreased creatinine clearance below 70 mL/min is significantly higher in our study than a UKPDS64 study, which showed 30.8% in a study of 5100 T2DM patients with 2 kidneys enrolled in it.[10] Also, the mean interval between both

development of DM and the evidence of nephropathy was significantly lower than the previously mentioned study being 5.7 and 10.1 years. This may be explained by the hyperfiltartion theory. The percentage of high albuminuria alone defined as urinary albumin creatinine ratio between 30 to 300 mg/g among the 43 diabetic donors was (32.6%) 17 donors. This percentage was higher than the 20% (1021 patients) in the 5100 T2DM patients with 2 kidneys enrolled in UKPDS64.[10] This may be explained by the previously described hyperfiltartion theory. The percentage of very high albuminuria alone defined as *urinary albumin creatinine ratio among the 43 diabetic donors above 300 mg/g* was 8 donors (18.6%). This percentage is higher than the 10% in a 5100 T2DM patients with 2 kidneys enrolled in UKPDS64.[10]

There is a positive correlation between diabetic donors BMI and urinary albumin creatinine ratio as shown in Figure 1 and Figure 2. So BMI is also considered as a risk factor for the development of high albuminuria, very high albuminuria, and/or decreased eGFR below 70 mL/min among donors. The percentage of high albuminuria among the 60 prediabetic donors was 16 donors (26.7%).

The percentage of diabetic donors with a family history of diabetes was (28 donors out of 43) (64.3%); 18 of them (64.2%) developed high or very high albuminuria the percentage which made our center question the acceptance of donors with positive family history of DM.

In our study, we compared diabetic donors on metformin containing regimens (17/43 diabetic donors) between other (nonmetformin) oral hypoglycemics containing regimens (15/43 diabetic donors). The mean urinary albumin creatinine ratio of the metformin group was significantly lower (P = .04), and the estimated creatinine clearance by CKD-EPI equation was significantly higher (P = .003) than the other oral hypoglycemic agents group. This may be one of the principle factors explaining the improvement of vascular outcome associated with metformin as in UKPDS 34.[11] Patients allocated metformin, compared with the conventional group, had risk reductions of 32% for any diabetes-related endpoint, 42% for diabetes-related death, and 36% for all-cause mortality including vascular complications. Among patients allocated intensive blood-glucose control, metformin showed a greater effect than chlorpropamide, or glibenclamide for any diabetes-related endpoint (P = .0034), all-cause mortality (P = .021), and stroke (P = .032) (UKPDS34).[11]

In comparing diabetic donors on insulin (14/43 diabetic donors) versus diabetic donors noninsulin containing regimens (29/43 diabetic donors), there was no significant difference between the mean estimated creatinine clearance of both groups. The mean urinary albumin creatinine ratio was significantly lower (P = .01) in the insulin group, which may reflect the beneficial effect of insulin on the vascular outcome that may be due to the anti-inflammatory and vasodilator effects of insulin. In the UKDPS 33,[12] the insulin group compared with 7.9% in the conventional group an 11% reduction. Compared with the conventional group, the risk in the intensive group was 12% lower for any diabetes-related endpoint; 10% lower for any diabetes-related death; and 6% lower for all-cause mortality. Most of the risk reduction in the any diabetes-related aggregate endpoint was due to a 25% risk reduction (P = .0099) in microvascular endpoints, including the need for retinal photocoagulation (UKDPS 33).[12]

References

1. Fuggle SV, Allen JE, Johnson RJ, et al; and the Kidney Advisory Group of NHS Blood and Transplant. Factors affecting graft and patient survival after live donor kidney transplantation in the UK. *Transplantation*. 2010;89(6):694-701.
2. Meyer C, Dostou JM, Welle SL, Gerich JE. Role of human liver, kidney, and skeletal muscle in postprandial glucose homeostasis. *Am J Physiol Endocrinol Metab*. 2002;282(2):E419-E427.
3. Defronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. *Diabetes*. 2009;58(4):773-795.
4. Shaefer CF. The Ever-Expanding Universe. *University Primary Care Physicians*. 2008;4:204-207.
5. Fehrman-Ekholm I, Gäbel H. Reasons for non-acceptance of living kidney donors. *Transplant Proc*. 1995;27(6):3526.
6. Sampson MJ, Drury PL. Development of nephropathy in diabetic patients with a single kidney. *Diabet Med*. 1990;7(3):258-260.
7. Hou S. Expanding the kidney donor pool: ethical and medical considerations. *Kidney Int*. 2000;58(4):1820-1836.
8. Levey AS, Stevens LA, Schmid CH, et al; and the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9): 604-612. Erratum in: *Ann Intern Med*. 2011;20;155(6):408.
9. David W, Cho NH, Guariguata lL, et al. *IDF Atlas*. 2013;6:80-89.
10. Adler AI, Stevens RJ, Manley SE, et al; and the UKPDS GROUP. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney Int*. 2003;63(1):225-232.
11. King P, Peacock I, Donnelly R. The UK prospective diabetes study (UKPDS): clinical and therapeutic implications for type 2 diabetes. *Br J Clin Pharmacol*. 1999;48(5):643-648.
12. [No authors listed] Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352(9131):837-53. Erratum in: *Lancet*. 1999;354(9178):602.