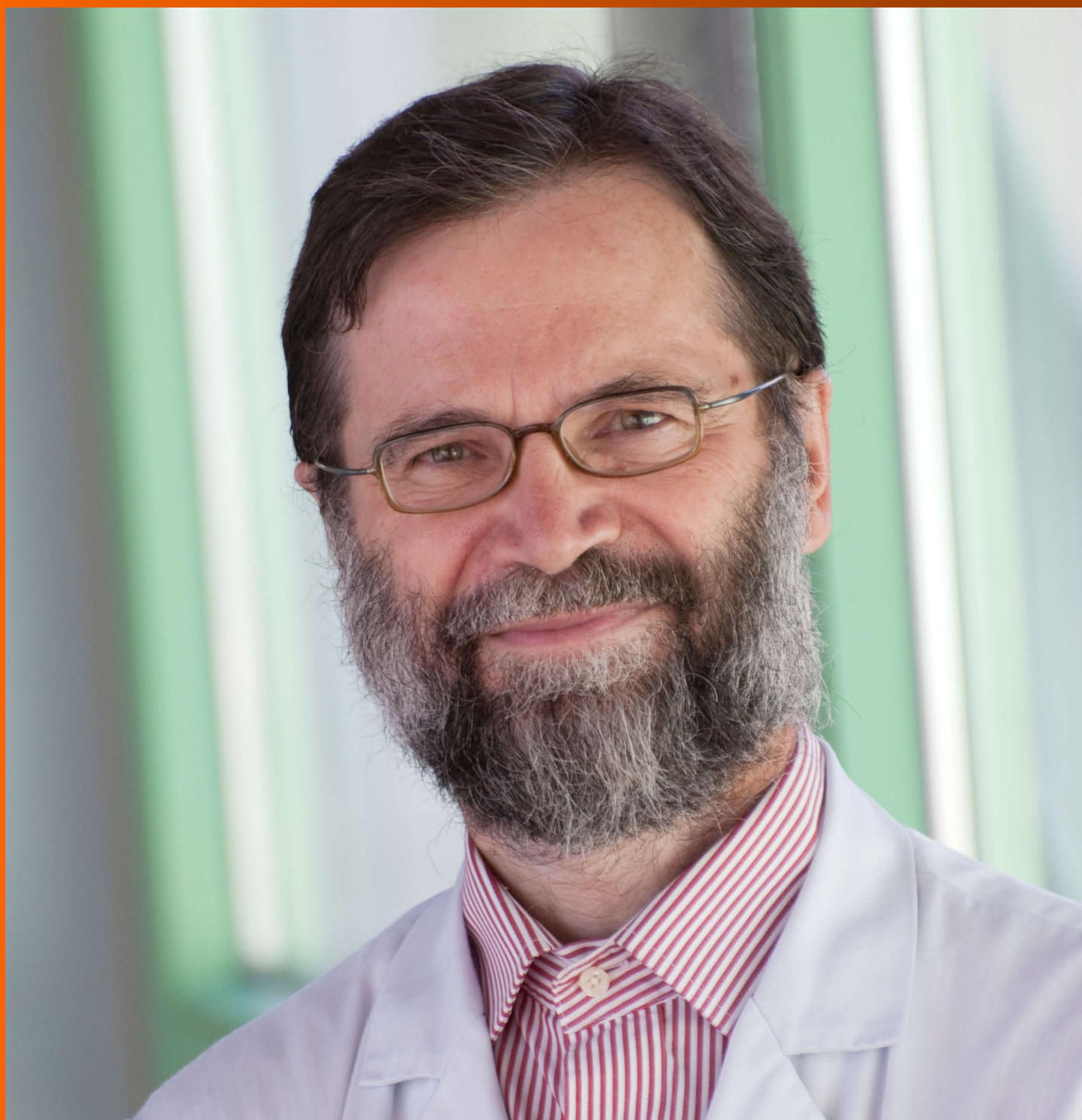


World Journal of *Transplantation*

World J Transplant 2017 April 24; 7(2): 103-160



**REVIEW**

- 103 Role of gastroesophageal reflux disease in lung transplantation
Hathorn KE, Chan WW, Lo WK
- 117 Intra-islet endothelial cell and β -cell crosstalk: Implication for islet cell transplantation
Narayanan S, Loganathan G, Dhanasekaran M, Tucker W, Patel A, Subhashree V, Mokshagundam S, Hughes MG, Williams SK, Balamurugan AN

MINIREVIEWS

- 129 Smoking in Renal Transplantation; Facts Beyond Myth
Aref A, Sharma A, Halawa A
- 134 Past, present and future of kidney paired donation transplantation in India
Kute VB, Patel HV, Shah PR, Modi PR, Shah VR, Rizvi SJ, Pal BC, Modi MP, Shah PS, Varyani UT, Wakhare PS, Shinde SG, Ghodela VA, Patel MH, Trivedi VB, Trivedi HL

META-ANALYSIS

- 144 Systemic meta-analysis assessing the short term applicability of early conversion to mammalian target of rapamycin inhibitors in kidney transplant
Kumar J, Reccia I, Kusano T, Julie BM, Sharma A, Halawa A
- 152 Living related and living unrelated kidney transplantations: A systematic review and meta-analysis
Simforoosh N, Shemshaki H, Nadjafi-Semnani M, Sotoudeh M

Contents

World Journal of Transplantation
Volume 7 Number 2 April 24, 2017

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Smoking in Renal Transplantation; Facts Beyond Myth

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Abstract

Smoking is one of the preventable leading causes of death worldwide. Most of the studies focused on the association between smoking and cardiovascular disease, pulmonary diseases, malignancy and death. However, the direct effect of smoking on the renal system was undermined. There are emerging evidence correlating tobacco use with pathological changes in the normal kidneys. The effect is more obvious on the renal allograft most probably due to the chronic immune suppression status and the metabolic effect of the drugs. Several studies have documented a deleterious effect of smoking on the renal transplant recipients. Smoking was associated with lowering patient and graft survival. Smoking cessation proved to improve graft survival and to a lesser extent recipient survival. Even receiving a renal transplant from a smoker donor increases the risk of death for the recipient and carries a poorer graft survival compared to non-smoking donors. Most of the studies investigating the effect of smoking were based on self-reporting questionnaires, which may be misleading due to poor recall or the desire to give socially acceptable answers. This made the need of a reliable biomarker of ultimate importance. Cotinine was proposed as a promising biomarker that may help to provide objective evidence regarding the status of smoking and the dose of nicotine exposure, yet there are still some limitations of its use. The aim of this work is to review the current evidence to improve our understanding of this critical topic. Indeed, this will help to guide better-designed studies in the future.

Key words: Smoking; Kidney donor; Kidney recipient; Renal transplantation

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Core tip: There are several studies addressing the effect

of smoking on different body systems, yet, there are only few exploring the effect of smoking on the outcome of renal transplantation. Our present article summarizes all the available data published over the past 2 decades for better understanding of this topic and may also guide future studies.

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INTRODUCTION

Smoking is a challenging health care problem; it has a well-established correlation with many serious medical conditions like cardiovascular diseases, pulmonary diseases, malignancy and death^[1]. Cigarette smoking assumes to have a role in atherosclerosis, endothelial dysfunction, progression of vascular disease progression of proteinuria, as it contains large amounts of free radicals^[2]. This makes smoking a significant renal risk factor, with considerable consequences on health care budget^[3].

The effect of smoking is aggravated in renal transplant recipients due to the effect of immune suppression medications on carcinogenesis, in addition to the effect of chronic kidney disease itself on cardiovascular risk and mortality^[1].

Despite the extensive smoking-related research, yet studies that investigated this phenomenon in the transplant populations are relatively few, and most of them are retrospective, poorly randomised or small sample size^[2].

EFFECTS OF SMOKING ON THE KIDNEY

The hazards of smoking were investigated thoroughly in association with cardiovascular disease, lung disease and oncogenesis. However, the effect of smoking on healthy kidney and progression of primary kidney diseases did not attract great attention^[3]. Indeed, many studies confirmed the role played by smoking in the progression of many intrinsic renal diseases (e.g., diabetic nephropathy, IgA nephropathy and autosomal dominant polycystic kidney disease)^[3].

Ritz *et al*^[4] studied the effect of smoking on healthy normotensive volunteers. They reported a significant increase in arginine vasopressin levels (from 1.27 ± 0.72 to 19.9 ± 27.2 pg/mL) and serum epinephrine (from 37 ± 13 to 140 ± 129 pg/mL). There was an increase in renal vascular resistance by 11% and a decrease in the glomerular filtration rate (GFR) by 15%. They assumed these effects are secondary to nicotine itself as these findings were reproduced by using nicotine containing gum^[4].

Pinto-Sietsma *et al*^[5] performed a leading cross-sectional study on 7476 participants to evaluate the effect of smoking on the development of albuminuria and abnormal kidney functions in non-diabetic population. They documented the presence of a dose-dependent association between smoking and development of both microalbuminuria and renal impairment in this screening. These findings were less obvious or absent in former smokers^[5].

RECIPIENT SMOKING AND TRANSPLANTATION OUTCOME

Smoking is strongly correlated to some of the potentially fatal outcomes, and there is some evidence that these complications are aggravated in solid organ transplant recipients^[6].

Smoking is a well-known risk factor for cardiovascular disease. Ponticelli *et al*^[7] have addressed the role of cardiovascular disease as the leading cause of death in renal transplant recipient. The development of de novo cardiovascular insult in the first year post-transplant was associated with pre-existing cardiovascular disease, older age, pre-transplant hypertension, smoking and duration of dialysis^[7].

The second leading cause of death post-transplantation was malignancy^[2,7] with a clear association between smoking and increased risk for certain types of malignancy^[1].

The effect of smoking on renal transplant recipients was investigated in relatively few studies, and most of them are retrospective. Table 1 summarises the results of most of these studies^[1,8-20].

It worth to mentioning that Zitt *et al*^[16] had a unique approach by studying the relation between smoking and renal biopsy findings of 76 kidney transplant recipients. Current smokers had an increase in the severity of vascular intimal fibrous thickening ($P = 0.004$). While the degree of chronic sclerosing nephropathy ($P = 0.05$) and arteriolar hyalinosis ($P < 0.001$) were associated with the duration of time post-transplantation^[16].

Most of these studies have revealed a clear benefit of smoking cessation on graft survival, but the effect on patient survival is less clear possibly reflecting the permanent atherosclerotic effect on the vascular system^[20].

EFFECT OF SMOKING HABIT OF KIDNEY DONOR ON THE OUTCOME OF TRANSPLANTATION

It may be logic that the recipient smoking will affect his own survival, but surprisingly, even the donor smoking will affect the recipient survival years after transplantation^[21,22].

Lin *et al*^[21] have analysed data from the United Network for Organ Sharing from 1994 to 1999, and

Table 1 The impact of smoking on kidney transplant recipient

| Ref. | Year | Study design | No. of cases | | Results | Conclusion |
|---|------|---------------------------------|--------------|---------------|--|---|
| | | | Total | smokers | | |
| Arend <i>et al</i> ^[8] | 1997 | Retrospective analysis | 916 | 394 | RR 2.2 of mortality after the first year of transplantation (95%CI) | The risk of mortality after the first year was higher in older patients, men, diabetics, hypertensive and smokers |
| Cosio <i>et al</i> ^[9] | 1999 | Retrospective analysis | 523 | 147 | Patient survival shorter in smokers by Cox regression ($P = 0.0005$), univariate and multivariate analysis ($P = 0.0004$) | History of smoking correlates with decreased patient survival, the effect of smoking on transplant recipient is quantitatively similar to the effect of diabetes |
| Kasiske <i>et al</i> ^[10] | 2000 | Retrospective analysis | 1334 | 330 | RR 1.3 of graft loss with smoking more than 25 pack/yr at transplantation (95%CI) and increase the risk of death (RR = 1.42, 95%CI) | The effect of smoking dissipates after five years from quitting |
| Doyle <i>et al</i> ^[11] | 2000 | Retrospective analysis | 206 | 155 | RR 8.1 for graft loss ($P < 0.001$) and RR 7.9 for mortality ($P < 0.001$) | Tobacco use was associated with worse patient and graft survival compared to those who never smoked or those who quit smoking at least two months before transplantation |
| Matas <i>et al</i> ^[12] | 2001 | Retrospective analysis | 2540 | Not mentioned | Pre-transplant smoking has RR 2.1 for graft loss | Pre-transplant smoking, peripheral vascular disease or dialysis more than one year were all associated with worse long-term outcome |
| Sung <i>et al</i> ^[13] | 2001 | Retrospective analysis | 645 | 156 | RR 2.3 for graft loss, graft survival in smokers <i>vs</i> non-smokers were (84% <i>vs</i> 88%) at 1 yr, (65% <i>vs</i> 78%) at 5 yr and (48% <i>vs</i> 62%) at 10 yr follow up ($P = 0.007$) | Smoking significantly affects graft survival, an effect that is not explained by increases in rejection or patient death. Smoking cessation has beneficial effect on graft survival |
| Yavuz <i>et al</i> ^[14] | 2004 | Retrospective analysis | 226 | 97 | There was no significant relation between pre-transplant smoking and graft loss ($P = 0.129$), or mortality ($P = 0.138$) | They suspected that the non-significant effect of smoking might be attributed to the limited number of cases included |
| Kheradmand <i>et al</i> ^[15] | 2005 | Retrospective analysis | 199 | 41 | Pre-transplant smoking was associated with reduced overall graft survival ($P = 0.01$) | Smoking contributes to graft loss but has no significant relation with rejection episodes |
| Zitt <i>et al</i> ^[16] | 2007 | Retrospective analysis | 279 | 62 | Smokers had higher serum creatinine levels. Transplant biopsy was indicated more often in smokers compared to non-smokers (39% <i>vs</i> 24%, $P = 0.02$) | Smoking was associated with vascular fibrous intimal thickening in transplanted kidneys so that it may have a role in the development of chronic allograft nephropathy and graft loss |
| Gombos <i>et al</i> ^[17] | 2010 | cross-sectional study | 402 | 102 | In spite that kidney functions in smokers were not affected after one month of transplantation, yet, there was significant lower kidney function in smokers after three years ($P < 0.05$). This correlates with the intensity of smoking ($P < 0.05$) | Smoking is common following kidney transplantation in Hungary, and this may be a risk of a poor long-term outcome |
| Nogueira <i>et al</i> ^[18] | 2010 | Retrospective analysis | 997 | 329 | Patient and graft survival were worse in smokers (AHR for patient survival was 1.6, 95%CI, $P = 0.02$, and graft survival AHR 1.47, 95%CI, $P = 0.01$). Glomerular filtration rate after one year was lower in smokers | History of smoking will negatively affect patient and graft survival. Also, it increases the risk of early rejection |
| Hurst <i>et al</i> ^[19] | 2011 | Retrospective analysis | 41705 | 5832 | New onset smokers have increased risk of graft failure (AHR = 1.46, $P < 0.001$) and death (AHR = 2.32, $P < 0.001$) compared with never smokers | New onset smoking post-transplant associated with lower patient and graft survival |
| Agarwal <i>et al</i> ^[20] | 2011 | Prospective observational study | 604 | 133 | Current smokers have increased risk of graft failure compared to recipients who never smoke (HR = 3.3, $P = 0.002$). While past smokers had an almost similar risk of graft failure compared to non-smokers (HR = 1.1, $P = 0.7$) On the other hand, current and past smokers were at higher risk of mortality compared to non-smoker recipients (HR = 2.1, 95%CI: 1.1-3.8, $P = 0.016$, and HR = 2.4, 95%CI: 1.4-4.0, $P = 0.001$, respectively) | Current smoking is a risk factor for graft failure and mortality Despite the finding that smoking cessation may not alter the risk of mortality, but at least it will improve the graft survival |

| | | | | | | |
|-----------------------------------|------|------------------------|-------|-------|---|---|
| Opelz <i>et al</i> ^[1] | 2016 | Retrospective analysis | 46548 | 15086 | Patients who quit smoking before transplantation had clear benefits regarding patient and graft survival when compared to those who continues to smoke (all-cause graft failure (HR 1.1 vs 1.5, $P < 0.001$), all-cause mortality (HR 1.1 vs 1.6, $P < 0.001$) and death with functioning graft due to malignancy (HR 1.4 vs 2.6, $P = 0.001$)) However, they still have a higher risk for graft loss, malignancy and death compared to those who never smoke before | Smoking cessation before transplantation improve patient and graft survival. There is also a substantial reduction in certain types of malignancy compared to those who continued to smoke (lower incidence of respiratory, urinary tract, female genital organs, lips and oral cavity tumours) |
|-----------------------------------|------|------------------------|-------|-------|---|---|

AHR: Adjusted hazard ratio.

they declared that smoking habit of the donor has mild, yet statistically significant effect on recipient survival (HR = 1.06, $P < 0.05$), and graft survival (HR = 1.05, $P < 0.05$).

Underwood *et al*^[22] studied a retrospective analysis of 602 kidney transplant recipients and their living donors. The effect of donor smoking on graft survival was statistically insignificant (HR = 1.19, $P = 0.515$), unlike the recipient smoking which proved to be significant (HR = 1.74, $P = 0.05$). However, the recipient survival was negatively correlated to donor smoking (HR = 1.93, 95%CI: 1.27-2.94, $P = 0.002$) and recipient smoking (HR = 1.74, 95%CI: 1.01-3.00, $P = 0.048$)^[22].

Heldt *et al*^[23] evaluated GFR of 100 living donors and their recipients, the recipients of smoking donors had lower calculated GFR (37.0 mL/min per 1.73 m² vs 53.0 mL/min per 1.73 m²; $P < 0.001$) at a mean follow-up of 38 mo.

SMOKING BIOMARKER AND RENAL TRANSPLANTATION

Smoking exposure and analysis of dose of smoking depends on self-reporting in most of the studies^[24], which we strongly believe it lacks accuracy. A proper estimation of the risks associated with tobacco use depends on accurate measurement of exposure, which may be difficult in certain population such as pregnant women and parents of young children, where smoking considered socially unacceptable^[24]. Some patients may not recall the number of cigarettes accurately (digit bias)^[25], and finally the tobacco dose differs between individuals due to the difference between cigarettes as well as the difference in inhaling habits (passive smoking)^[25]. All these factors made the development of a valid and accurate biomarker for tobacco smoking of ultimate importance.

Cotinine is the major metabolite of nicotine. It has a relatively constant level due its long half-life (16 h vs 2-3 h for nicotine), which can be measured in plasma or urine. For these reasons, cotinine is considered a promising biomarker of smoking exposure^[25].

Hellemons *et al*^[25] studied 603 renal transplant recipients for a mean follow-up of 6.9 years. The aim was to investigate the relation of self-reporting and cotinine exposure in transplant population and to

evaluate the use of cotinine as an alternative for self-report^[25]. They concluded that active smoking had a negative impact on patient and graft survival, while former smokers had increased the risk of mortality but not graft failure. They documented that cotinine measurement (especially plasma cotinine) provides a valid alternative to self-reported smoking exposure, and it may even be preferred over self-reporting in epidemiological studies^[25].

The use of cotinine also has its limitations. Cotinine level is a reflection of smoking over the past few days, and this may be misleading if the patient is smoking occasionally (like in weekends) or if the patient was smoking less due to a period of illness. The second limitation lies in its inability to differentiate between never-smoking and former-smoking^[25]. Differentiating never-smoking from former-smoking is clinically relevant as former-smoking was proved to be associated with increasing risk of recipient mortality^[20,25].

We believe that the combination of cotinine measurement and self-reporting of smoking exposure will be the most reliable approach in evaluating renal transplant population.

CONCLUSION

Smoking remains a major modifiable health care challenge; it is the leading cause of variable morbidities and mortality. The use of smoking biomarkers proved to be reliable in evaluation and quantification of smoking exposure in the transplant population. Donor smoking and recipient former smoking proved to have a negative impact on survival. Transplant community should pay more attention to donor and recipient smoking cessation programs.

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