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REVIEW

Infertility, pregnancy and breastfeeding in kidney transplantation recipients: Key issues

Mohamad Habli, Dawlat Belal, Ajay Sharma, Ahmed Halawa

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Abstract

Chronic kidney disease (CKD), especially in advanced stages, is an important cause of infertility. In CKD patients, infertility has been linked to multiple factors. The pathophysiology of infertility related to CKD is complex and forked. Correction of modifiable factors can improve fertility in both genders. In males as well as females, successful kidney transplantation offers good chances of restoration of reproductive function. In female renal allograft recipients, recovery of reproductive functions in the post-transplant period will manifest as restoration of normal menses and ovulation. Owing to this improvement, there is a significant risk of unplanned pregnancy, hence the need to discuss methods of contraception before transplantation. In kidney transplant recipients, different contraceptive options for pregnancy planning, have been used. The selection of one contraception over another is based on preference and tolerability. Pregnancy, in renal transplanted females, is associated with physiologic changes that occur in pregnant women with native kidneys. Immunosuppressive medications during pregnancy, in a recipient with a single functioning kidney, expose the mother and fetus to unwanted complications. Some immunosuppressive drugs are contraindicated during pregnancy. Immunosuppressive medications should be discussed with renal transplant recipients who are planning to breastfeed their babies. In addition to antirejection drugs, other medications should be managed accordingly, whenever pregnancy is planned.

Key Words: Infertility; Chronic kidney disease; Pregnancy; Kidney transplantation;

Immunosuppression; Breastfeeding

Core Tip: Chronic kidney disease (CKD) is a major cause of infertility in both sexes. Multiple factors amplify infertility in CKD patients. Kidney transplantation can restore fertility in men and women. Menses will return in the majority of females after kidney transplantation. This improvement increases the risk of accidental pregnancy, so contraception should be discussed in advance. Kidney transplant recipients utilize several contraceptives to plan pregnancy. Preference and tolerability determine contraception choice. If pregnancy occurs, transplanted women experience the same physiologic changes as pregnant women with native kidneys. During pregnancy, immunosuppressive drugs can cause consequences. Breastfeeding kidney transplant recipients should discuss immunosuppressive and other medicines.

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INTRODUCTION

Chronic kidney disease, especially in advanced stages causes fertility and sexual dysfunction in males as well as in females[1] (Figure 1). The male sexual health malfunction manifests as erectile dysfunction in up to 80% of end-stage renal disease (ESRD) patients on hemodialysis[2]. The pathophysiology is due to a combination of vascular calcification, accelerated atherosclerosis, uremic neuropathy, impairment of the hypothalamic-pituitary-testicular axis and secondary hyperparathyroidism[3]. ESRD is also with alteration in the levels of sex hormones which include reduction in testosterone level and elevation in luteinizing hormone (LH) and follicle-stimulating hormone (FSH)[4]. The prevalence of infertility in females, of childbearing age, with ESRD, has been reported as high as 92%[5].

Factors that are implicated in the pathogenesis of infertility in women with ESRD include impairment at the level of the hypothalamus-pituitary-ovarian axis manifesting as high FSH and LH and low estrogen levels[6], menstrual disorders in up to 75% of patients manifesting as amenorrhea, oligomenorrhea or functional menopause[7], and abnormal endometrial atrophy due to reduced estrogen level [8]. Other contributions to infertility include reduced libido and orgasmic impairment, in addition to vaginal dryness or failure of vaginal lubrication[9], as shown in Figure 2[10].

Improvement of fertility in patients with kidney disease is achieved by correction of modifiable factors like anemia, hyperparathyroidism, dialysis adequacy[11], avoidance of toxic medications[12], and hormonal replacement therapies[13], However, kidney transplantation remains the best option for the management of infertility due to ESRD for both genders[14].

Following successful kidney transplantation, the function of the hypothalamic-pituitary-gonadal axis is gradually restored leading to normalization of sex hormone levels in men and women in the majority but not in all patients[15,16]. In males, this recovery manifests as improvement in erectile dysfunction, libido, and spermatogenesis, whereas in women as restoration of menses and ovulation[16].

Owing to the improvement in reproductive functions and sexual health within 3-6 mo, these patients should be counselled about the significant potential of conceiving shortly after successful kidney transplantation. Hence it is imperative to explain contraception during the pre-transplantation assessment so that pregnancy can be planned at a time when the risk to mother and fetus is minimal *i.e.*, after one year of uneventful kidney transplantation.

IMPACT OF PREGNANCY ON GRAFT SURVIVAL

Intra-renal hemodynamics is reported to be altered, starting from the 1st week of pregnancy, due to a reduction in vascular resistance[17], increase in cardiac output[18], and increase in plasma volume[19], which finally lead to an increase in renal blood flow[20] and subsequently increase in GFR. In normal pregnancy with native kidneys, GFR increases along with an increase in renal size[19,21]. Despite volume expansion and increase in cardiac output, mean arterial blood pressure is reduced by about 10-15 mmHg in the 1st trimester and then returned to normal by the 2nd trimester[22].

It is well established that acute kidney injury can occur during pregnancy in non-transplant females due to pregnancy itself. Pregnancy-related acute kidney injury can also happen in the transplanted

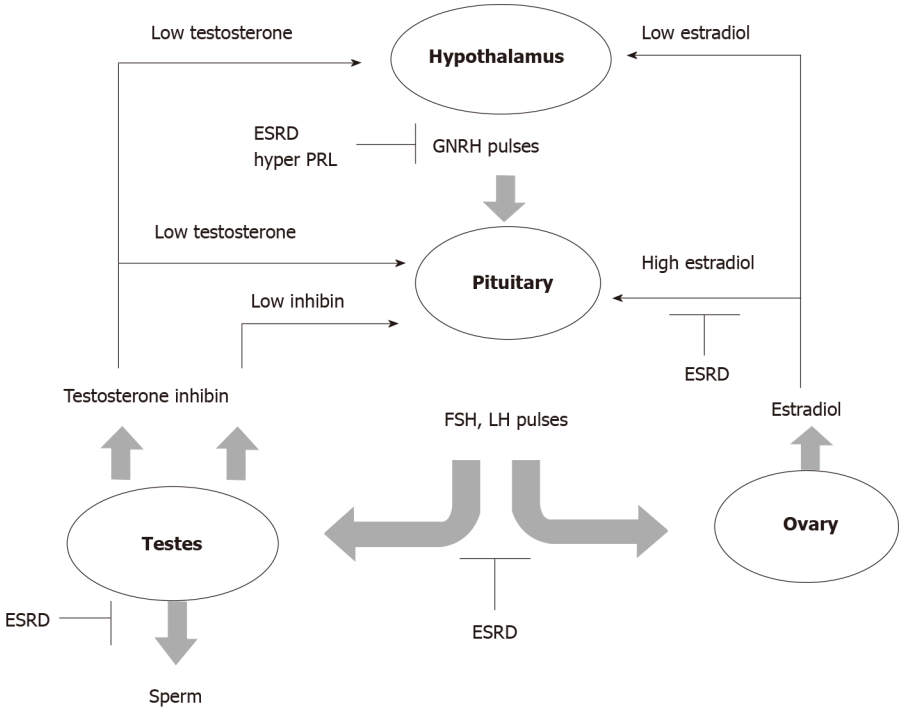

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Figure 1 The hypothalamic-pituitary-gonadotropin axis in men and women with end-stage renal disease. ESRD: End-stage renal disease; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone.

allograft, however, when it occurs it affects not only the pregnant patient but also the fetus. Refer to Figure 3[23].

Several studies evaluated the impact of pregnancy on graft survival. Levidiotis *et al*[24], using ANZDT Registry data of pregnancy in transplant recipients, demonstrated that the delivery of first live birth was comparable between the study group and control group, and was not associated with worse twenty-year graft survival.

Rahamimov *et al*[25] evaluated the long-term impact of pregnancy on allograft and patient survival and reported that graft and recipient survival did not differ from the control group in the follow-up.

Shah *et al*[26] conducted a systemic review and meta-analysis about pregnancy outcomes in kidney transplant recipients. They reported that the rejection rate during pregnancy was 9.4% which is comparable to the United States mean of 9.1%.

To evaluate possible bias in patients' selection that may affect outcomes and interpretation of results, M. Pappias and colleagues evaluated pregnancy outcomes after living kidney donation in a systematic review. In this study, 2 authors used the Risk of Bias In Non-randomized Studies of Interventions (ROBINS-I) method to evaluate participant selection, exposure, and results. Robvis online software plotted risk-of-bias evaluations. Grading of recommendations, assessment, development, and evaluations method graded study certainty. As a result, authors concluded that after donation, the absolute chance of pregnancy related and associated complications remain minimal, which is comparable to other studies[27].

In conclusion, pregnancy is not associated with worse graft outcomes in kidney transplanted recipients, however, female recipients should be carefully selected before pregnancy planning and should be counseled about possible complications. Stability of kidney function at time of pregnancy detection, should be monitored attentively throughout the course of pregnancy.

IMPACT OF TRANSPLANTATION ON THE OUTCOME OF PREGNANCY

Although the majority of female recipients restore their ability to conceive, pregnancy rates are much lower when compared to the general population[24,28,29]. Gill *et al*[28] demonstrated that the rate of pregnancy in transplanted females was less than 1/3 of the general population in the first 3 years following transplantation surgery.

Shah *et al*[26], based on a meta-analysis of the outcomes of pregnancy in transplanted patients, reported an increased risk of gestational diabetes and gestational hypertension. Preeclampsia was reported to be sixfold higher in transplant women. Shah *et al*[26] reported higher rates of preterm delivery, stillbirths, and neonatal death. Other pregnancy-associated complications such as induced

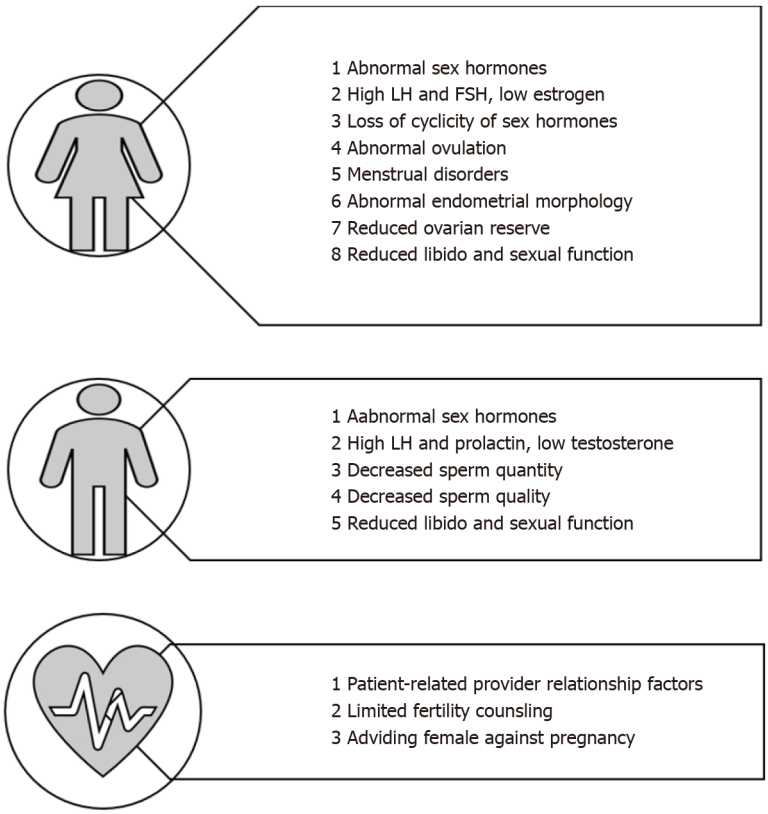

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Figure 2 Male and Female factors implicated in the development of infertility in chronic kidney disease patients. FSH: Follicle-stimulating hormone; LH: Luteinizing hormone.

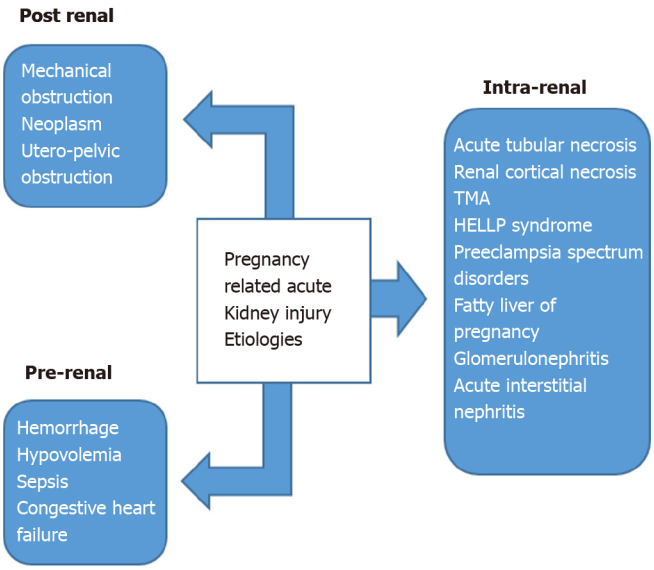

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Figure 3 Pregnancy related acute kidney injury etiologies. TMA: Thrombotic microangiopathy; HELLP: Hemolysis, elevated liver enzymes and low platelet.

abortions, miscarriages and ectopic pregnancies were reported to be more common in kidney transplant recipients.

Deshpande *et al*[29] reported a live birth rate among pregnant renal transplant recipients comparable to that of the general population. Other retrospective studies have reported live birth rates of up to 79% [30,31]. Preterm delivery was reported to occur in 46% of recipients[30].

Cesarean delivery was significantly more frequent in the transplant population reaching 43%-72%, although no clear evidence to support this practice[29-31]. The United Kingdom Transplant Pregnancy Registry, showed a higher rate of low birth weight in 20% to 50% of cases[30,31].

MANAGEMENT OF IMMUNOSUPPRESSION

T-lymphocyte-depleting agents and IL-2 inhibitors (basilixumab) are commonly used as induction therapy for transplant patients. Maintenance therapy is commenced in the hospital and continued to prevent acute rejection. Before conception, modification of immunosuppression is frequently needed, as some drugs have shown to be associated with adverse outcomes in the pregnancy and fetus[32].

In addition to female recipient preparation for pregnancy, male recipients who desires paternity should be also properly counseled about the impact of immunosuppression on fertility. Few studies have reported the negative effect of immunosuppressive drugs, particularly sirolimus, on male fertility. Sirolimus was shown to be linked to reduced fertility following kidney transplantation, due to its toxic effect on the sperm[33,34]. That's why, unrecovered fertility in male recipients maintained on mammalian target of rapamycin inhibitors (mTORi) following renal transplant surgery, should raise the suspicion of possible drug toxicity.

In the other hand, maintenance immunosuppression in females is modified to avoid teratogenic effect on the fetus. Generally, Mycophenolate Mofetil (MMF)/Mycophenolic Sodium (MPS) is considered unsafe during pregnancy. Kidney transplant recipients who are on MMF during pregnancy are at higher risk of pregnancy loss in the first-trimester first trimester along with severe congenital fetal structural malformations[35-37]. Following exposure to MMF, congenital malformations such as ear, eye, and lip/palate malformations have been reported in 23%-27% of live births[38]. Therefore, MMF should switch over to azathioprine that is, not associated with maternal or fetal risks[39].

Calcineurin inhibitors are the cornerstone of maintenance immunosuppressive therapy in any kidney transplant recipient. Calcineurin inhibitors (CNIs) have been evaluated during pregnancy in renal transplant females. The use of tacrolimus in kidney transplanted pregnant is considered safe. Physiologic changes during pregnancy can alter some pharmacokinetic properties of tacrolimus, that's why frequent monitoring of tacrolimus levels is recommended[40]. Furthermore, several studies have examined the effect of cyclosporine on the fetus and demonstrated that it is not teratogenic[41,42]. However, the Food and Drug Administration (FDA) categorizes Cyclosporin as category C, which indicates that human risk cannot be excluded. CNIs, in particular tacrolimus, are associated with increased risk of Post-transplant Diabetes Mellitus. It is well established that tacrolimus is more diabetogenic than cyclosporine[43,44]. Increased tacrolimus levels have been strongly linked to altered glucose tolerance, toxic effect on islet cells with subsequent development of diabetes mellitus. In pregnant recipients treated with tacrolimus with new onset hyperglycemia, shifting to safer drug such as cyclosporine could be an option. However, a recent systematic review and meta-analysis compared the impact of cyclosporine and tacrolimus on pregnancy outcomes in liver/kidney transplant recipients, found no significant differences in the incidence of gestational diabetes between them[45].

The use of mammalian target of rapamycin (mTOR) inhibitors is considered a contraindication during pregnancy. Sirolimus should be discontinued at least 12 wk before pregnancy, while everolimus should be discontinued at least 8 wk before conception. Boulay *et al*[46], and Framarino *et al*[47]. Reported limited data on the use of mTOR inhibitors in pregnant patients.

With the increased use of co-stimulation blocker, Belatacept, in non-pregnant recipients, there is still no clear evidence on the safety of its use in pregnant recipients[48].

In conclusion, the combination of calcineurin inhibitors, azathioprine and steroids is the mainstay maintenance therapy in pregnant recipients, as no major fetal or maternal effects have been reported.

APPROACH TO THE USE OF COMMON NON-IMMUNOSUPPRESSION DRUGS

Hypertension is reported to be more common in pregnant transplant recipients accounting for 20%-70% compared to 1%-5% in pregnant women in the general population[26,30,49]. Hypertension in pregnant transplant recipients, is associated with a higher risk of preeclampsia and eclampsia.

In hypertensive pregnant females, medications such as labetalol[50], calcium channel blockers of dihydropyridine group[51], methyldopa[52], and hydralazine[53] can effectively manage hypertension with a safe profile regarding the pregnant transplant recipient and fetus.

Non-dihydropyridine calcium channel blockers (such as diltiazem and verapamil), should not be administered with calcineurin inhibitors, because of their effect on enzyme CYP3A4 metabolism[54].

Angiotensin-converting enzyme inhibitors, angiotensin receptor inhibitors, and direct renin inhibitors are not acceptable during pregnancy because they are associated with significant fetal risk[55]. Therefore, it is recommended to plan conception at least 6 wk after discontinuation of these drugs.

There is very limited data on the safety of angiotensin-converting enzyme inhibitors in normal lactation. The minimal concentration of angiotensin converting enzyme inhibitors, in breast milk, can cause hemodynamic instability in premature infants and neonates in therapeutic doses. Captopril and Enalapril are excreted in very low doses in breast milk and considered safe with breastfeeding, nonetheless, babies should be monitored for adverse events[56].

Thiazide and loop diuretics use during pregnancy, have not been linked to increased risk of fetal unfavorable outcomes, when prescribed for volume overload and elevated blood pressure. Diuretic usage should be limited, because of major concern about affecting physiologic volume expansion during pregnancy[57].

In the other hand, antibiotics during pregnancy are used more frequently, as the incidence of infections is higher in transplanted patients, owing to the use of potent immunosuppression. Urinary tract infections are prevalent in female transplant patients, and the risk rises by up to 40% during pregnancy, presumably due to physiologic anatomic changes occurring in the urinary tract[58]. The prescription of antibiotics in kidney transplant recipients should always be considered for a potential interaction and possible adverse effects. Antibiotics such as Nitrofurantoin, Amoxicillin, Cephalexin, Cefpodoxime and Fosfomycin are considered safe in pregnancy in kidney transplant recipients with no drug-drug interaction[59]. Ciprofloxacin and Trimethoprim/Sulfamethoxazole are generally not recommended in pregnancy with and without transplantation. Antibiotics that are generally used for the management of upper and lower tract infections include macrolides, quinolones, penicillins and cephalosporins. Clarithromycin, but not azithromycin should be avoided in kidney transplant recipients irrespective of pregnancy, because of its effect on the hepatic/intestinal enzyme CYP3A4 metabolism and subsequent increase in tacrolimus level and possible toxicity. Azithromycin is safe to use during pregnancy in renal transplant recipients, but attention should be paid to the risk of arrythmia as both drugs increase QTc interval. The use of quinolones in pregnancy is still controversial in literature because of concerns on their adverse effects on the fetus formation. However, animal studies did not show an increase in major birth defects, abortion or maternal complications[60]. Hence, quinolones can be prescribed in complicated and life threating infections.

Penicillins and cephalosporins are generally acceptable in kidney transplant recipients in the context of pregnancy.

IMPACT OF KIDNEY TRANSPLANTATION AND PREGNANCY ON THE INCIDENCE OF INFECTION AND OUTCOMES

After kidney transplantation, infection is the second major cause of mortality among transplant patients, behind cardiovascular disease. Up to seventy percent of kidney transplant recipients will encounter an infection episode during the first three years following transplantation, according to estimates[61]. As mentioned earlier, bacterial urinary tract infections are more prevalent during pregnancy in a kidney transplant recipient because of potent immunosuppression used.

Other than urinary tract infection, pregnant transplant recipients are at risk of TORCH infections. TORCH infections are a category of infectious disorders that can be transmitted to a newborn during pregnancy, delivery, or shortly after birth. Toxoplasmosis, rubella, cytomegalovirus, herpes, and others are termed as TORCH. In transplant recipients, the risk of cytomegalovirus infection during pregnancy is minimal, as conception is often planned 1-2 years following transplantation. Congenital cytomegalovirus (CMV) is the leading nongenetic cause of congenital sensorineural hearing loss and neurological impairment[62,63]. Therefore, it is essential that CMV infections be monitored.

Another TORCH virus, Herpes simplex virus can occur during pregnancy in immunocompromised patients as primary infection or activation of latent infection. In case of herpetic infection valacyclovir or acyclovir can be used safely during pregnancy. Caesarean delivery in infected mothers reduces the incidence of newborn herpes 1 or 2. Therefore, caesarean section should be performed if cervical cultures show herpes. To prevent primary varicella-zoster virus (VZV) infection after transplantation, pretransplant screening for past VZV infection should be conducted, and naive patients should be immunized with live attenuated varicella vaccine if possible[58].

Toxoplasmosis in pregnant transplant recipients can be caused by either reactivation of a latent infection or primary infection. In a fitting clinical setting, toxoplasmosis should be evaluated in the differential diagnosis of pneumonia, culture-negative sepsis, and encephalitis. Toxoplasmosis should be screened quarterly in pregnant kidney transplant patients. Sulfadiazine, pyrimethamine and spiramycin should be given to immunosuppressed individuals with growing antibody titers to prevent congenital toxoplasmosis infection[64].

As a conclusion, many illnesses can be avoided or ameliorated by pre- and post-transplant care, pretransplant screening of infections and updated immunization remain the major standard of treatment. Protocol polymerase chain reaction screening of CMV, BK virus and others, in the post-operative period has been also shown to reduce the incidence of infectious complications. Finally, most opportunistic infections occurring in pregnant transplanted patients can be preventable, therefore, transplant nephrologists carry a major responsibility in the delivery of best available medical care for all

patients.

IMPACT OF PROTEINURIA AND KIDNEY DYSFUNCTION ON THE ALLOGRAFT SURVIVAL IN PREGNANT KIDNEY TRANSPLANT RECIPIENTS

Pregnancy in transplant patients with stable kidney function and no risk factors is associated with favorable graft outcomes. The graft failure rate in pregnant transplanted women was comparable to that in non-pregnant allograft recipients at a follow-up of ten years[65]. Renal transplant recipients with hypertension, pre-gestational elevated creatinine, and proteinuria are at higher risk to develop accelerated graft loss.

National Transplantation Pregnancy Registry revealed that recipients who faced graft loss in five years had lower eGFR at baseline before pregnancy, higher serum creatinine after pregnancy, and a higher rejection rate three months after pregnancy[66]. Recurrent acute rejections with renal impairment before and during pregnancy increase the risk of graft failure.

The likelihood of graft failure at five years was significantly higher when serum creatinine was > 1.3 mg/dL pre-pregnancy. Serum creatinine at > 1.6 mg/dL was associated even with a more than 7-fold higher risk of graft failure. Keitel *et al*[67] reported that pre-pregnancy creatinine was > 1.5 mg/dL in all recipients who experienced graft failure 2 years following childbirth.

Schwarz and colleagues also reported poor graft outcomes in patients with low eGFR before or during pregnancy[68].

Proteinuria before or during pregnancy, especially proteinuria of > 1 g/d, is associated with worse graft survival[69]. Higher the proteinuria, the higher the risk of premature birth, Intrauterine growth retardation, and miscarriages. Hence, it is strongly recommended to achieve low proteinuria levels below 500 mg before pregnancy to avoid adverse events[69].

CONTRACEPTION OPTIONS FOR KIDNEY TRANSPLANT RECIPIENTS

Despite the fact that end-stage renal disease negatively affects fertility, there is a recovery of reproductive function after a kidney transplant, and pregnancy is common. Fertility can be efficiently reverted in the few months after a kidney transplant. Hence, to guarantee that pregnancies do not occur prior to maternal optimization, it is crucial that women with a history of kidney transplants plan their pregnancies and have access to adequate contraception[70]. Female recipients should be educated about contraceptive methods which could be selected based on old experience, medical history, comorbidities, and preference[71].

Irreversible contraception is usually achieved by surgical procedures like vasectomy[72,73], or tubal ligation[74,75]. Reversible contraception is achieved using an intrauterine device (IUD), hormonal pills/injections or patches and other barrier methods.

Hormonal contraceptives are commonly used and highly effective with a minimal failure rate[76]. Estrogen-based contraceptives are associated with exacerbation of migraines, the risk of venous thromboembolism (VTE), and worsening hypertension control. Depo medroxyprogesterone (DMPA) is an effective and safe contraceptive method, with prolonged effect over 3 mo. The use of DMPA increases the risk of VTE[77]. Other hormonal contraceptives include etonogestrel implant[78], transdermal patch and others.

IUDs are highly effective, easy to insert and low failure rate with no increased risk of VTE. IUDs are not associated with an increased risk of infectious complications[79].

The vaginal ring is another effective method of contraception. It is associated with a lower incidence of adverse events[80].

Barrier methods include condoms, spermicides, diaphragm, cervical caps and sponges are associated with failure rates due to compliance issues. Education of couples on its correct use may reduce the failure rate[81]. In conclusion, there is no study comparing the efficacy of different types of contraception in transplanted females. Therefore, an individualized approach to contraception is recommended, based on comorbidities, associated risk, and preference. A comparison of the effectiveness of contraceptive methods is demonstrated in Figure 4[82].

POST-TRANSPLANT BREASTFEEDING

Pregnancy in a kidney transplant recipient remains to be complicated because of the detrimental effects of immunosuppressive therapy on the renal allograft, fetus and the transplant recipient. The safety of immunosuppression therapy on breastfed babies was addressed in a few studies[83-100]. There is reassuring data on the use of calcineurin inhibitors based regimen in addition to prednisone and azathioprine during lactation. Prednisolone is excreted at very low levels in breast milk. The studied

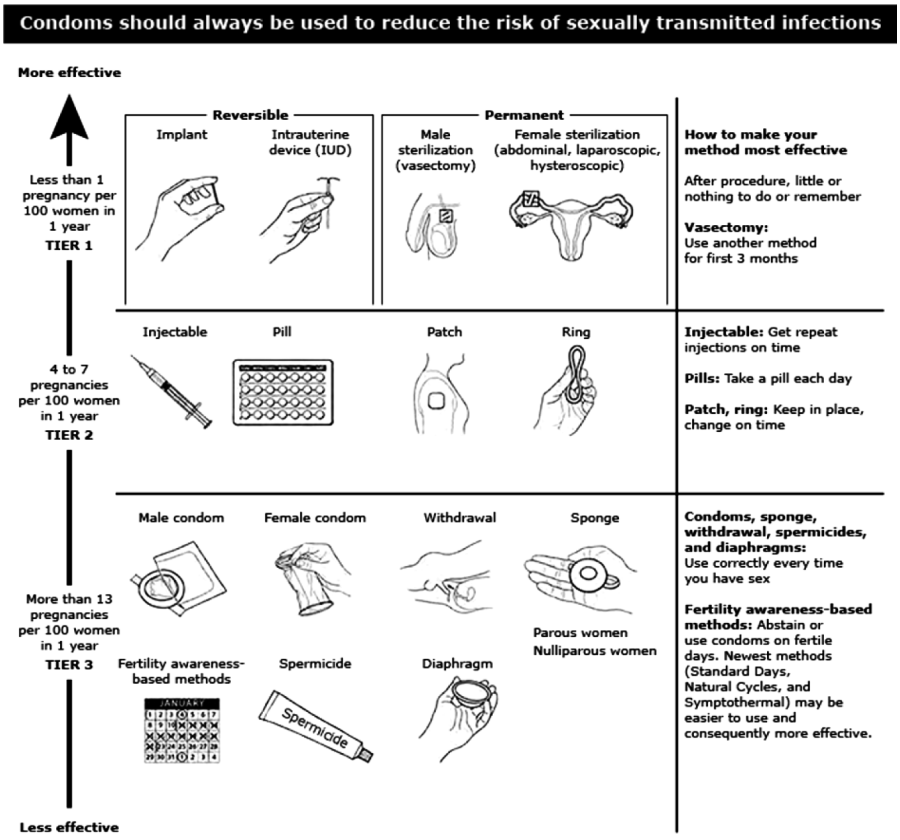

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Figure 4 Different contraceptive methods options for pregnancy planning in kidney transplant recipients.

dose of 50 mg/d was not shown to affect growth. The risk of infections or hematological complications in infants is not increased[31].

Regarding azathioprine, its metabolites were undetectable in the breast milk and there was no side effect noted in the infants. Infants of mothers receiving azathioprine did not show any significant increase in infection rate[84-88].

Cyclosporine was reported to have minimal excretion in breast milk. The study showed no nephrotoxic effect, growth retardation or immunosuppressive effects on the baby. Another study demonstrated undetectable Cyclosporine levels in breastfed babies from mothers on Cyclosporine[89-96]. Tacrolimus levels were undetectable in infants. Studies demonstrated that lactation in renal transplant recipients on tacrolimus was safe but needs close monitoring of the infant[97-100].

As mTORi are contraindicated during pregnancy, it is also advised not to initiate mTORi during lactation, as there are no studies that support this practice[101]. MMF usage in breastfeeding was not studied in humans, however, results extrapolated from animal studies demonstrated harm[35]. Belatacept was suggested by transplant experts not to be used while breastfeeding as no study evaluated its effect on infants[102].

CONCLUSION

As ESRD is associated with infertility, kidney transplantation offers the best option to restore sexual health and the ability to conceive. Proper contraception and pregnancy planning are mandatory, to avoid unwanted pregnancy and the toxic effects of immunosuppression on the fetus. Modifications in immunosuppression are essential before conception. Normal lactation is the best feeding for babies, but patients on immunosuppressive drugs should be counseled about their possible side effects. Normal delivery is considered the normal way of delivery, although practice patterns may differ.

Primary care physicians and nephrologists should make a greater effort to discuss menstrual and reproductive issues with women who have received a kidney transplant. The transplant team should provide complete information and counseling to women of childbearing age who are considering pregnancy.

Finally, pregnancy is generally considered safe in the setting of kidney transplant, however, a team approach to care that includes the primary care physician, a transplant nephrologist, and a qualified obstetrician in high-risk pregnancies, is crucial for a successful pregnancy and better outcomes.

FOOTNOTES

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MINIREVIEWS

Pancreatic fat in type 2 diabetes: Causal or coincidental?

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Abstract

Type 2 diabetes (T2D) is a multifactorial metabolic disorder affecting more than 450 million people across the globe. With the increasing prevalence of T2D and obesity, the role of fat accumulation at sites other than subcutaneous adipose tissue has received significant attention in the pathophysiology of T2D. Over the past decade and a half, a pressing concern has emerged on investigating the association of pancreatic fat accumulation or pancreatic steatosis with the development of disease. While a few reports have suggested a possible association between pancreatic fat and T2D and/or impaired glucose metabolism, a few reports suggest a lack of such association. Pancreatic fat has also been linked with genetic risk of developing T2D, prediabetes, reduced insulin secretion, and beta cell dysfunction albeit some confounding factors such as age and ethnicity may affect the outcome. With the technological advancements in clinical imaging and progress in assessment of pancreatic beta cell function, our understanding of the role of pancreatic fat in causing insulin resistance and development of various etiologies of T2D has significantly improved. This review summarizes various findings on the possible association of pancreatic fat accumulation with the pathophysiology of T2D.

Key Words: Type 2 diabetes; Pancreatic fat; Steatosis; Glucose metabolism; Beta cell function; Non-alcoholic fatty pancreas disease; Obesity; Insulin resistance

Core Tip: The concomitant rise in the incidences of obesity and type-2 diabetes (T2D) has increased interest in understanding the role of pancreatic fat accumulation or pancreatic steatosis in causing T2D. In the past few years, various researchers have attempted to decipher whether pancreatic fat has any causative role in the pathogenesis of T2D. While a few cross-sectional and retrospective studies have shown a positive association between pancreatic fat and T2D, there is a lack of well-controlled, prospective, and long-term follow-up studies that could clearly establish the role of pancreatic fat in causing T2D. Therefore, in light of the presently available evidence, the role of pancreatic fat as an independent predictor of T2D must be interpreted with caution.

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INTRODUCTION

The global increase in the incidence and prevalence of type 2 diabetes mellitus (T2D) has been linked to a parallel epidemic of obesity observed during the last few decades. This association of T2D and obesity has brought research interest in adipose tissue biology with gradual conceptual changes, and adipose tissue is no longer considered an inert lipid store but rather a metabolically active endocrine organ with an enormous capacity to secrete numerous metabolically active compounds and hormones[1-3].

In obese individuals, when storage capacity in adipose tissue is overwhelmed by the circulating lipids, progressive and abnormal accumulation in non-adipose tissue results in steatosis, which may involve the liver, skeletal tissue, heart, and pancreas[4,5]. Accumulating lipid droplets within cells may result in cellular dysfunction and cell death, also known as lipotoxicity[6]. Further, human studies suggest that lipid content in hepatocytes and skeletal tissue is a more important determinant for insulin resistance than circulating free fatty acids[7]. Although obesity-related ectopic fat deposition in the liver, primarily caused by non-alcoholic fatty liver disease (NAFLD), and its relationship with metabolic syndrome and T2D have been studied extensively, ectopic fat accumulation in other organs, especially the pancreas, and their clinical significance have received little attention from the researchers until recently.

Ogilvie first described the term "pancreatic lipomatosis" to denote excessive fat accumulation in pancreatic tissue. After that, various terminologies were used to describe the same, which include pancreatic steatosis, fatty infiltration or replacement, fatty pancreas, and non-alcoholic fatty pancreas disease (NAFPD)[8]. However, pancreatic fat accumulation or steatosis may also be seen in nonobese individuals due to various other etiologies, including chronic alcohol use, viral infections, chemotherapy, and cystic fibrosis[8,9]. Therefore, some authors suggested restricted use of the term NAFPD for those cases of pancreatic steatosis which are associated with metabolic syndrome and obesity, as this condition may be reversed by weight loss or the use of certain medications[9-11]. Whereas, in the other situations where irreversible fatty replacement occurs following acinar cell death, the preferred terminology used is 'fatty replacement'[9]. Table 1 depicts the nomenclature used to describe accumulation of fat in the pancreas[9,12]. The pancreas can be roughly sub-divided into endocrine pancreas containing islets and exocrine pancreas that is responsible for secretion of digestive enzymes, and is comprised of lobes, segregated by connective tissues. Pancreatic fat accumulation involves intralobular or interlobular adipocyte infiltration or presence of intracellular lipid droplets[13,14].

The association between T2D and NAFPD is controversial. Some studies reported more pancreatic fat accumulation in T2D subjects than in those without diabetes, while others reported no difference[15-17]. In this review, we will discuss the epidemiology of NAFPD, the pathophysiology of pancreatic fat accumulation in T2D, its relationship with T2D, and the effect of anti-diabetic medications on pancreatic steatosis.

EPIDEMIOLOGY

The studies documenting the true global prevalence of pancreatic steatosis are limited[18]. Besides, the available data is highly variable, affected largely by the ethnicity and age of the population being studied and the modality used for the detection of pancreatic fat[19]. Accordingly, the prevalence of pancreatic steatosis in the general population is estimated to be roughly between 16% to 35%[3-6,20-23]. In a recently conducted cross-sectional study in Japan, the prevalence of pancreatic fat accumulation, as determined using transabdominal ultrasonography, was 46.8%. Amongst the subjects with pancreatic steatosis, there was preponderance of males and subjects with higher prevalence of lifestyle-related

Table 1 Nomenclature of pancreatic fat accumulation

Name	Definition
Pancreatic steatosis or fatty pancreas or pancreatic lipomatosis	General terminology for accumulation of pancreatic fat
Lipomatous pseudohypertrophy	An extreme form of pancreatic fat accumulation with uniform or focal enlargement of the pancreas and replacement of exocrine system by adipose tissue which is unrelated to obesity
Fatty replacement	Replacement with adipocytes following death of pancreatic acinar cells
Fatty infiltration	Obesity-related infiltration of the pancreas with adipocytes
NAFPD	Pancreatic fat accumulation along with obesity and metabolic syndrome
Non-alcoholic fatty steatopancreatitis	Pancreatitis resulting from accumulation of pancreatic fat

NAFPD: Non-alcoholic fatty pancreas disease.

diseases, including fatty liver disease[7,24].

A systemic review and meta-analysis involving over 12000 individuals showed a prevalence rate of 33% [95% confidence interval (CI): 24%-41%]. The results of meta-regression showed that the prevalence of pancreatic steatosis was associated with hypertension, T2D, and metabolic syndrome. Of note, 9 of 11 studies included in this study were conducted in Asian populations, thereby raising questions regarding the generalizability of the data[8,25]. More studies in different ethnic populations, especially those with high rates of obesity and metabolic syndrome, would be valuable in delineating the true global prevalence of pancreatic steatosis.

DIAGNOSIS OF NAFPD

Pancreatic enzymes are rarely raised in NAFPD, therefore, serological investigations are not useful in diagnosing NAFPD. There are various imaging modalities available, however, there are certain challenges associated with the use of these technologies in diagnosing NAFPD, as listed below.

Transabdominal ultrasonography: It is a widely available and non-invasive method of pancreatic fat assessment. It detects pancreatic steatosis as an increase in echogenicity within the pancreatic parenchyma, as compared to renal and hepatic echogenicity. This is an operator dependent procedure and presence of overlying bowel gas shadow and obesity may interfere with the visualization and interpretation of pancreatic steatosis[26].

Endoscopic ultrasound (EUS): It is an invasive endoscopic procedure, which allows good visualization of the pancreas. Various studies have revealed the relationship between increased pancreatic echogenicity and the presence of obesity and fatty liver[22,27]. This modality is also limited by operator dependency. Further, apart from NAFPD, the presence of pancreatic fibrosis may also result in increased echogenicity of pancreatic parenchyma, thus resulting in false positive interpretation[28].

Computed tomography (CT): Fat infiltration in the pancreas is detected as hypodensity (in Hounsfield units) as compared to the adjacent spleen[29]. However, this method is also operator dependent. Saisho *et al*[16] demonstrated that CT evaluation using fat/parenchyma ratio is a useful method to detect NAFPD.

Magnetic resonance imaging (MRI): MRI is the most preferred method for detecting pancreatic steatosis at present. It is non-invasive, safe, and highly sensitive for detecting pancreatic fat. Its accuracy in identifying pancreatic steatosis is comparable with that of histopathological examination[30,31].

MRI proton density fat fraction: This modality allows quantification of pancreatic fat with high accuracy[32].

PATHOPHYSIOLOGY OF PANCREATIC FAT ACCUMULATION

Obesity has been implicated as the most important risk factor for NAFPD[33]. Increased BMI in human studies was found to be associated with pancreatic fat accumulation[21]. Moreover, animal studies in mice models revealed that obesogenic diets for mothers during pregnancy and lactation might result in NAFPD through alterations in circadian metabolic patterns and endoplasmic reticulum stress[34,35]. In obesity, both mechanisms of pancreatic steatosis, *i.e.*, fat replacement (adipocytes replacing dead acinar cells) and fat infiltration (*i.e.*, fat accumulation), go hand in hand[9].

Age and male sex are other risk factors for NAFPD[36]. Evidence from epidemiological studies indicates a positive association of NAFPD with age[36,37]. NAFLD is another important risk factor for

pancreatic steatosis. Lee *et al*[38] found a concurrence rate of 67.9% between NAFPD and NAFLD, with a high negative predictive value for NAFLD (96.4%) in patients with a normal pancreas. Uygun and colleagues reported a strong association between non-alcoholic steatohepatitis (NASH) and NAFPD. About half of these patients with NASH had concurrent NAFPD[39]. In contrast to the above finding, another study reported that NAFPD was significantly associated with advanced stage of hepatic fibrosis but lacked any correlation with NASH[40].

Besides, sedentary lifestyle, smoking, consumption of excessive meat, hypertension, hyperferritinemia, and low lipase activity in serum are other potential risk factors for pancreatic steatosis[20-22,41-43]. The various risk factors for NAFPD are summarised in Figure 1.

While the association between obesity and NAFPD has been conclusively demonstrated, the underlying mechanism remains unclear. Contemporary research on NAFPD mainly focuses on the prevalence and clinical implications, but the literature is scarce regarding genetics and underlying molecular mechanisms. However, some evidence points towards the role of adipocyte-derived cytokines and inflammatory factors in the pathogenesis of NAFPD, particularly those induced by free fatty acids (FFAs). Animal studies in rats revealed that FFA-induced hyperlipidemia was associated with increased expression of tumor necrosis factor (TNF-α), interleukin (IL-6), and monocyte chemoattractant protein-1 (MCP-1) with a significant simultaneous increase in body fat[44,45]. An *in vitro* study has shown that palmitic acid (a saturated FFA) could induce increased expression as well as secretion of IL-6 and IL-8, which was associated with a significant increase in intracellular fat content[46]. However, there is some contradictory evidence as well. In a recent *ex vivo* study on blood mononuclear cells, palmitic acid, γ-linolenic acid, and arachidonic acid were found to have minor effects on the gene expression of pro-inflammatory factors, including TNF-α, IL-6, and cyclooxygenase-2, whereas, oleic acid, α-linolenic acid, and docosahexaenoic acid reduced the expression of these genes[47]. Further research in this area is warranted to draw some meaningful conclusions.

Further, progressive accumulation of pancreatic fat may have a role in the pathogenesis of pancreatic cancer. This hypothesis was endorsed by a study which showed relation between high-fat diets and pancreatic cancer risk[48]. There is also evidence in the literature which revealed a direct association between pancreatic steatosis and the incidence of pancreatic cancer[49,50].

Influence of adipocyte-derived factors on beta cell function

Adipocytes and preadipocytes secrete adiponectin and leptin, respectively[51]. The direct effect of adiponectin and leptin on beta-cell survival and function has been studied widely using *in vitro* models and are detailed in several reviews[52-55]. Adiponectin secreted from the adjacent adipocytes acts on beta cells *via* the adiponectin receptor 1 and thereby promotes beta cell survival and insulin secretion. Leptin secreted from preadipocytes acts on the leptin receptor in a paracrine fashion, resulting in inhibition of insulin release.

Sympathetic stimulation and fasting state result in adrenaline and glucagon secretion, which in turn leads to activation of β-adrenergic receptors and glucagon receptor on adipocytes, respectively, with a consequent increase in lipolysis and release and local elevation of fatty acids[56]. In acute conditions, fatty acids act on fatty acid receptor 1 (FFAR1/GPR40) and stimulate insulin release from the beta cells [57]. However, when chronically elevated, fatty acids at high concentrations may lead to endoplasmic reticulum stress and beta cell apoptosis[58,59]. Fatty acids can also act on the Toll-like receptor 4 (TLR4) and mediate beta cell death and islet inflammation[55,60]. TLR4-dependent activation of IL-8 and MCP-1 results in monocyte chemotaxis. Besides, activation of TLR4 on tissue macrophages induces the cytotoxic cytokine IL-1β release resulting in beta cell death[60].

ASSOCIATION OF PANCREATIC FAT AND T2D

Studies showing association of pancreatic fat with T2D

With respect to pancreatic fat accumulation, several studies have reported its positive association with the development of T2D[39] (Table 2). In 2007, Tushuizen *et al*[15], reported the association between beta cell dysfunction and pancreatic fat content, leading to T2D development for the first time. The authors observed higher median pancreatic fat content in T2D subjects as compared to age and BMI matched controls (20.4% *vs* 9.7%, P = 0.032). However, they noted a significant association of pancreatic fat content with beta cell dysfunction in non-diabetic controls, rather than in patients with T2D. These findings suggest that pancreatic fat accumulation may contribute to beta cell dysfunction and T2D development in susceptible individuals and once overt diabetes sets in, additional factors may account for further decline in beta cell function. Nevertheless, all subjects demonstrated that pancreatic fat content had an inverse correlation with insulinogenic index and beta-cell glucose sensitivity. The findings suggest that pancreatic fat accumulation might contribute to the development of T2D, although the results need to be validated in larger cohorts[15]. A cross-sectional study in 2013 by Ou *et al*[37], found that NAFLD participants were more likely to acquire prediabetes [odds ratio (OR) = 1.798, 95%CI: 1.544-2.094] or diabetes (OR = 2.578, 95%CI: 2.024-3.284). Amongst all subjects, those with fatty pancreas were associated with diabetes (OR = 1.379; 95%CI: 1.047-1.816) as well as prediabetes (OR = 1.222;

Table 2 Studies showing association or lack of association between pancreatic fat and type 2 diabetes

S.No.	Title	Inference/key observation	Ref.
Studies showing association of pancreatic fat with T2D			
1	Pancreatic fat infiltration, β-cell function and insulin resistance: A study of the young patients with obesity	Elevated blood glucose levels and reduced beta cell function (HOMA-β and IGI) were reduced in subjects with HPF	Wen *et al*[65], 2022
2	Association of pancreatic fat content with type II diabetes mellitus	Elevated fat content in the pancreatic tail region may identify patients at risk for T2D	Nadarajah *et al* [64], 2020
3	Pancreatic steatosis associates with impaired insulin secretion in genetically predisposed individuals	Pancreatic fat leads to impairment of beta-cell function in subjects at genetic risk for diabetes	Wagner *et al* [66], 2020
4	Longitudinal association of fatty pancreas with the incidence of type-2 diabetes in lean individuals: a 6-year computed tomography-based cohort study	Lean subjects with fatty pancreas can lead to development of T2D	Yamazaki *et al* [67], 2020
5	Association of pancreatic steatosis with chronic pancreatitis, obesity, and type 2 diabetes mellitus	T2D is associated with higher pancreatic fat along with visceral and subcutaneous adiposity	Tirkes *et al* [62], 2019
6	Pancreatic fat content is associated with β-cell function and insulin resistance in Chinese type 2 diabetes subjects	Male subjects with T2D, demonstrated positive association between pancreatic fat content and insulin resistance	Lu *et al*[63], 2019
7	The effect of fatty pancreas on serum glucose parameters in patients with non-alcoholic steatohepatitis	NASH patients with high pancreatic fat had impairment in glucose metabolism	Uygun *et al* [39], 2015
8	Pancreatic fat and β-cell function in overweight/obese children with non-alcoholic fatty liver disease	Association of higher pancreatic fat content in subjects with prediabetes as compared to non-diabetic NAFLD obese children	Pacifico *et al* [61], 2015
9	The association between non-alcoholic fatty pancreas disease and diabetes	NAFLD and fatty pancreas were linked to diabetes, irrespective of age, gender, obesity, or other cardiometabolic risk factors	Ou *et al*[37], 2013
10	Pancreatic fat content and β-cell function in men with and without type 2 diabetes	Inverse correlation of pancreatic fat content with insulinogenic index and beta-cell glucose sensitivity in all the study subjects	Tushuizen *et al* [15], 2007
Studies showing lack of association of pancreatic fat with T2D			
1	Lack of independent association between fatty pancreas and incidence of type 2 diabetes: 5-year Japanese cohort study	No independent association between T2D and pancreatic fat was observed upon correction for possible confounders such as BMI and hepatic attenuation	Yamazaki *et al* [68], 2016
2	Pancreatic adipose tissue infiltration, parenchymal steatosis and beta cell function in humans	Pancreatic fat was related to age, but not to blood glucose levels. No association between pancreatic fat and insulin secretion or beta cell activity in T2D subjects was observed	Begovatz *et al* [71], 2015
3	Ethnic differences in pancreatic fat accumulation and its relationship with other fat depots and inflammatory markers	No correlation between pancreatic fat and beta cell function was observed, during intravenous glucose tolerance tests in obese normoglycemic adolescents	Lê *et al*[69], 2011
4	Ectopic fat storage in the pancreas, liver, and abdominal fat depots: impact on β-cell function in individuals with impaired glucose metabolism	Pancreatic fat was increased in individuals with impaired glucose tolerance, without any direct relation with β-cell function	van der Zijl *et al*[70], 2011
5	Clinical implications of fatty pancreas: correlations between fatty pancreas and metabolic syndrome	Association between pancreatic fat and insulin resistance was mediated by visceral adiposity	Lee *et al*[38], 2009
6	Pancreas volumes in humans from birth to age one hundred taking into account sex, obesity, and presence of type-2 diabetes	Pancreatic fat levels increases with aging and obesity; however, it remained unchanged in subjects with T2D	Saisho *et al* [16], 2007

HPF: High pancreatic fat; HOMA-β: Homeostasis model assessment of β-cell function; NASH: Non-alcoholic steatohepatitis; NAFLD: Non-alcoholic fatty liver disease; T2D: Type 2 diabetes; IGI: insulinogenic index.

95%CI: 1.002-1.491), particularly in males. Similarly, an observational study in obese children with NAFLD by Pacifico *et al*[61] reported a significantly higher pancreatic fat content in subjects with prediabetes (3.60%) as compared to non-diabetic subjects (1.90%).

Over the last 5 years, the number of studies demonstrating the association between pancreatic fat content and T2D development has been on the rise. A retrospective study by Tirkes *et al*[62] in 2019, reported a direct association between pancreatic fat accumulation and fat within the visceral compartment. Subjects with T2D had higher pancreatic steatosis and elevated subcutaneous fat content. A retrospective study by Lu *et al*[63] in 2019, reported that T2D subjects (n = 78) had more pancreatic fat in comparison to non-diabetic subjects (n = 35) (pancreatic fat content 7.06% *vs* 5.36%). The pancreatic fat content had a positive association with insulin resistance and abnormal glucose metabolism as assessed by oral glucose tolerance test (OGTT) in male T2D subjects. The authors also reported that subjects with shorter diabetes duration were associated with insulin resistance and beta cell dysfunction. Another retrospective study by Nadarajah *et al*[64] in 2020, was performed to determine

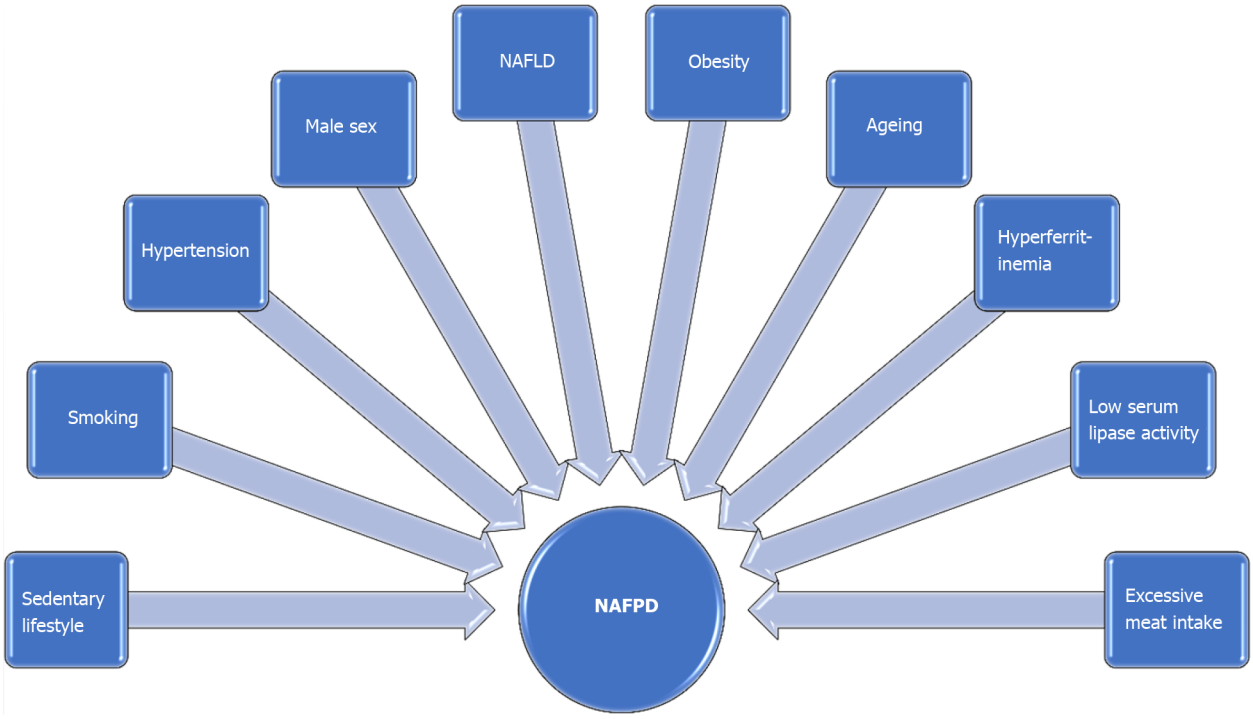

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Figure 1 Implicated risk factors for non-alcoholic fatty pancreas disease. NAFPD: Non-alcoholic fatty pancreas disease.

the association between regional pancreatic fat content and the risk of developing T2D. A significant difference was observed in the fat content in the pancreatic head, pancreatic body, and pancreatic tail in subjects with T2D and healthy controls, respectively. Upon regression analysis between the healthy control and prediabetes group, a significant difference was observed between fat content in the pancreatic tail region (OR = 1.1, 95%CI: 1.026–1.178; P = 0.007). ROC curve analysis showed an 81.3% specificity and 45.5% sensitivity in predicting the development of T2D within 4 years in subjects with fat content > 10% in the pancreatic tail region. Recently, a retrospective study in obese young subjects was performed, where pancreatic fat content was analysed by IDEAL-IQ MRI, on the basis of which the subjects were subgrouped as having high pancreatic fat (HPF) (> 6.2%) and normal pancreatic fat (NPF) (< 6.2%). The early and total insulin secretion during OGTT, *i.e.*, $AUCINS_{0\text{-}120}/AUCGLU_{0\text{-}120}$, was reported to be significantly reduced in the HPF group when compared with the NPF group (6.41 *vs* 16.01). Further, the subjects with HPF had significantly higher glucose levels during OGTT and the beta cell function in terms of homeostasis model assessment of β-cell function (HOMA-β) and insulinogenic index was also significantly reduced[65].

The genetic background has also been implicated in influencing pancreatic fat accumulation and insulin secretion. Subjects with a high genetic risk of T2D reported an increase in pancreatic fat content associated with lower insulin secretion by Wagner *et al*[66] in 2020. Upon multivariate regression analysis, insulin secretion was observed to be negatively correlated with pancreatic fat and genetic risk score for T2D. Therefore, based on the intensity of the genetic risk score of T2D, pancreatic fat may have a different association with insulin secretion. Recently, a retrospective cohort study by Yamazaki *et al* [67] in 2020, demonstrated a strong link between high levels of pancreatic fat and T2D in lean individuals. Subjects with low pancreas attenuation (< 46.9 HU) on CT were reported to have fatty pancreas and the incidence of T2D (4.13%) was higher at lower pancreas attenuation levels in lean individuals. Upon regression analysis, a strong association between pancreas attenuation and T2D incidence was observed (OR = 2.62, in subjects with fatty pancreas and OR = 1.20, in subjects with normal pancreas). A similar association was observed when P/S (ratio of pancreas attenuation to spleen attenuation) & P-S (difference between pancreas attenuation and spleen attenuation) were calculated.

Studies showing lack of association of pancreatic fat with T2D

While some of the cross-sectional observational studies have noted the association of NAFPD with T2D, controversies exist in this regard (Table 2). There is some evidence that also suggests that NAFPD may be a marker of beta cell dysfunction rather than a causative factor for the same.

Saisho *et al*[16] in 2007 reported that pancreatic fat, as measured by CT scans and at autopsy, increased with aging and obesity; however, it did not increase in T2D. Although most of the previously reported studies showing the association of pancreatic steatosis with T2D are cross-sectional in nature, the literature is sparse in regards to longitudinal studies. Yamazaki and colleagues, in a retrospective

cohort study, did not find an independent association between T2D and pancreatic steatosis as the association disappeared after the results were adjusted for potential confounders, including BMI and hepatic attenuation[68].

Many authors also did not find any independent association of pancreatic steatosis with marker of insulin resistance, the pathophysiologic hallmark of T2D. Lê *et al*[69] in 2011 did not observe any significant association between pancreatic fat fraction and markers of insulin sensitivity in obese individuals. They also noted that visceral adipose tissue and circulating free fatty acids were the most important determinant for pancreatic steatosis. In another study, pancreatic steatosis was found to be associated with visceral fat and HOMA-IR. However, after adjustment for the visceral fat area, the correlation with insulin resistance disappeared. It suggests that the association between pancreatic fat and insulin resistance was mediated by visceral adiposity. This observation revealed that a fatty pancreas might be a merely associated finding with generalized visceral adiposity[38].

Beta cell failure is required for transition from prediabetes to overt T2D stage. As far as beta cell function is concerned, most human and animal studies have shown an inverse relationship with pancreatic fat accumulation; however, contradictory evidence also exists.

van der Zijl *et al*[70] in 2011 demonstrated that the impairments in beta cell function as assessed by the hyperglycaemic clamp in patients with prediabetes were accompanied by pancreatic fat accumulation; however, they failed to show any relation between pancreatic steatosis and beta cell function. Lê *et al*[69] also did not find any correlations between pancreatic fat fraction and markers of beta cell function as assessed during intravenous glucose tolerance tests in obese normoglycemic adolescents. Further, no relations were observed between pancreatic fat infiltration and beta cell function across the spectrum of glucose tolerance in another study[71].

CONCLUSION

With the first report on pancreatic fat accumulation or pancreatic steatosis emerging as early as in 1933 [9], it took over 60 years to suggest a possible link between pancreatic steatosis and T2D, when van Geenen *et al*[72] in 1984 hypothesized that obesity and the associated insulin resistance are implicated in the infiltration of adipocytes in the pancreas. The studies conducted thereafter, established the fact that pancreatic fat accumulation is a major manifestation of metabolic syndrome, a common denominator in pathogenesis of T2D as well. The concept is still evolving and it is only after the studies in the past decade and a half that the picture is getting clearer. Several cross-sectional studies and a very few longitudinal studies have shown a positive association of pancreatic steatosis with T2D, however, BMI and NAFLD remain as potential confounders. Although the advancements in imaging technologies have now improved assessment of pancreatic fat content, there is a dearth of well-controlled prospective studies indicating functional consequences of pancreatic steatosis, especially in terms of insulin resistance and/or beta cell function.

Next, the age and population specific variations add to the complexities in correlating pancreatic fat with pathophysiology of T2D. Nevertheless, the emerging data suggests that pancreatic fat is an important contributing factor in the pathogenesis of T2D. Data from studies in lean subjects- and use of dynamic tests like OGTT and advanced methods of assessment of beta cell function indicate that pancreatic fat accumulation can predict development of T2D to some extent. Whether or not obesity, especially visceral obesity, is the initiating factor in causing pancreatic steatosis leading to T2D again remains to be seen. However, T2D being a multifactorial entity with varying genetic predispositions, the role of pancreatic fat must be interpreted with caution after taking into considerations various other factors associated with pathogenesis of T2D.

Finally, the concomitant increase in the incidence and prevalence of obesity and T2D worldwide necessitates the need for well controlled longitudinal cohort studies to stratify the role of pancreatic fat as an independent predictor of T2D.

FOOTNOTES

Author contributions: Mukherjee S and Maheshwari D performed the literature search and wrote the manuscript; Pal R wrote a portion of the manuscript; Sachdeva N drafted the structure of the manuscript and edited the whole manuscript.

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