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RENAL TRANSPLANTATION – BACKGROUND, GENETIC BASIS, AND FUTURE PROSPECTS

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ABSTRACT

Renal transplantation is a useful process of replacing an unhealthy kidney with a healthy donor kidney. It is used for treatment of end-stage renal disease, allowing most patients to return to a satisfactory quality of life. Renal transplantation is preferred over hemodialysis and peritoneal dialysis in terms of long term survival of the patients with end stage renal disease (ESRD). The factors contributing to chronic kidney disease (CKD) in children differ from those of adult onset CKD. The discovery of novel genes in early-onset CKD opens up new ways for finding clinical diagnostic methods. The patients suffering with steroid-resistant nephrotic syndrome (SRNS) represent another class of patients who are more prone to end-stage renal disease. Moreover, the congenital anomalies related to kidney and urinary tract (CAKUT) mainly can lead to CKD, and later on to ESRD requiring renal transplant as a form of renal replacement therapy. This review highlights prevalence, genetic basis and future prospects for achieving more success in renal transplantation.

KEYWORDS: SRNS, CAKUT, CKD, hemodialysis, peritoneal dialysis.

BACKGROUND AND INTRODUCTION

Renal transplantation is a clinical procedure used to transfer a healthy kidney from a live donor into a person with a dysfunctional kidney. Kidney is one of the important two bean shaped organ located near spine. The main function of kidney is to remove the excess waste from the body through urine.

Kidney transplant can be classified into two types: a). from living donors, b). from non-living donors. Currently, the number of live kidney donations has increased generally.[1] In some of the recent observations, the comparison among donors with healthy subjects and diseased persons showed the clear difference in success of procedure.[2,3] Moreover, such findings has raised many concerns related to long-term safety of donated organ.

The renal transplantation with live donor organs is associated with longer graft survival and therefore patient survival. Also, it has been observed that patients receiving an early transplant will be able to survive for a longer time

By transplantation, the survival rate of patients requiring the renal replacement therapy will be increased. However, in patients above 70 years of age the chances of survival will be less. Up till now, only fewer findings are available which indicate the benefits of transplantation over dialysis in this age group.

Translational research is an emerging science used to implement knowledge from basic biology to clinical research methods for common use. It starts with a simple idea testing in the laboratory with a success of bringing into clinical world. Kidney transplantation has been the focused area of research at present. Understanding the treatment adherence after kidney transplantation is a necessary process.

According to recent reports, out of 69 countries reporting transplantation statistics, an actual increase of almost 50% has been observed in kidney donation. The highest rate was reported in Saudia Arabia among a population of 32 million. The average number of patients suffering from kidney disease has been increased as much from the previously reported cases.[4] Although, success in transplantation will only be achieved by active decision for transplant.

The chances of organ wastage are more if patients immune system is not able to give a positive response. Further, it was reported from previous studies, the

average rate in US is nearly 20%-40% and 8% in Europe.[5-8]

The patients suffering from permanent loss of kidney functions suffers from chronic kidney disease (CKD). This results in loss of kidney function completely with the passage of time. The number of reported cases of CKD every year have been increased tremendously in the present time. Certain factors are responsible for this increase. Diseases like diabetes, anemia, and hypertension are among few of the commonly responsible causes of kidney disease. An effective control of Diabetes and hypertension can prevent or slow down the damage to the kidneys and thus prevent the progression to CKD and the ESRD. CKD is emerging as a major disease harmful for human health and is rapidly growing day by day in Pakistan. Patients suffering from CKD are more prone to risk of getting other diseases. The previously reported data showed greater risk of cardiovascular disease,[9,10,11] The risk is dependent on several factors including age and sex.[12] Conditions related to arterial stiffness leads towards increased chances of cardiovascular disease risk.[13,14] Anemia is another disease associated with CKD. This is caused by deficiency of one or more type of blood cells. However, the intensive care and on time precautionary measures play an important role in early diagnosis and treatment of anemia in CKD.

The major diseases contributing for CKD are diabetes and hypertension. The ratio is same in all high-income and most of the middle-income countries. Symptoms of all kidney diseases vary according to age, sex and certain other environmental factors. However, it was reported that, people suffering from CKD die early in premature stage as compared to people with end stage CKD.

Genetic basis of Kidney Disease

To study the genetic basis of disease, it is essential to understand its cellular mechanism, evolution, and classification etc. The kidney diseases can also be due to single gene defects. Several mutations have been identified in these genes. One of the most common example of mutations is podocin, which is contributing almost 15% in adults and nearly 25% in children. Some of the mutations are responsible for causing disease with 100% risk. To study the disease pathology, mechanism and treatment ways and to develop new target drugs is the need of the running time.

The kidney diseases are mostly linked with single gene mutations and reffered as mendelian disorders. The modern technology has helped to identify these diseased genes. The use of such techniques including, whole genome sequencing and genetic mapping has led to early discovery of mutated genes. At present, 36 mutated genes identified in Congenital anomalies of the kidney and urinary tract (CAKUT) and 39 genes in steroid resistant nephrotic syndrome (SRNS). [15-20] These studies suggested that, almost 25% of patients with early onset CKD can be identified by mutation analysis. Results are represented in table 1 below:

Table 1: Shows diseases with known genes causing mutations.

Disease	Known Genes	Mutations Identified
Steroid-resistant nephrotic syndrome	39	33%
CAKUT	36	25%

CAKUT was reported in 6-9 per 1000 births and serve as the leading cause of renal failure in children [21-23] The structural malformations of kidney and urinary tract emerging resulted from CKAUT includes renal agenesis, pelviureteric junction obstruction and ureterovesical junction obstruction. Up till now, more than 20 diseases genes have been identified for humans. Out of which 12% are dominant CAKUT genes responsible for causing kidney malfunctioning.[24-26]

Nephrotic syndrome, is characterized by edema, proteinuria and considered as one of the most important glomerular disease in children.[27-28] The patients suffering with SRNS have much complications. To treat such patients is more difficult. Moreover, number of different genes have been reported with mutations responsible for causing kidney diseases. Few of them are given in the table 2 below.

Table 2: Shows genes responsible for causing SRNS.

Genes	Disease	Function
NPHS1	Congenital nephrotic syndrome/SRNS	Cell-cell signaling
NPHS2	Congenital nephrotic syndrome/SRNS	Cell-cell signaling
CD2AP	FSGS/SRNS	Cell-cell signaling
ACTN4	Proteinuria	Cross-linking bundles of actin filament in the slit diaphragm
PLCE1	autosomal recessive nephrotic syndrome	Production of abnormal protein
TRPC6	FSGS	regulates mechano sensation at the slit diaphragm

CONCLUSION

Renal transplantation is useful to improve quality of life in patients suffering with end stage renal disease. The rate of survival after kidney transplantation largely depends on environmental and somehow to certain genetic factors. To increase the number of kidneys available for transplantation, methods need to be optimized and proper handling should be a concern. Patients suffering from CKD and nephrotic syndrome

represent major population. To understand the genetic basis and profile of patients, it is important to unravel the pathophysiological mechanism of disease. This can be achieved by applying principles of latest research methods.

Future Prospects

To attain quality of life, one of the key factor is proper monitoring of transplanted patient. In fact, quality of life changes according to therapeutic results. Further, the modern genetic techniques will provide deep insights to understand the disease. The use of target drugs and latest technologies has gained much more importance for disease therapy and diagnosis. However, this is also important to identify candidate genes, understand their molecular pathways under control of clinical features. Renal transplantation provides a quality life to many patients and is well-established treatment for treatment of end stage renal disease. Still, with advancement in medical technology, the number of positive and successful transplantation patients can be increased tremendously. For arrangement of more donors, the social surveys, and awareness campaigns will leads to more success in renal transplantation.

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