

Full Length Research Paper

Efficacy of renal precursor stem cells in management of chronic kidney disease: a cohort study

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In spite of tremendous achievements of modern medical science, chronic kidney disease (CKD) is still considered to be an untreatable pathology. CKD is caused by various etiological factors and is characterized by progressive deterioration of renal function due to loss of functioning nephrons. In absence of definitive treatment, CKD imposes a threat of end-stage renal failure with further necessity of dialysis and kidney transplant. In this article, we present a combined data on application of stem cell therapy in patients with CKD stages 3a and 3b. The influence of precursor cell implantation on parameters of renal profile is studied in a group of 23 patients with CKD stage 3a and 3b. Results of stem cell implantation were evaluated 6 months and 1 year after the procedure. 78.5% of patients with CKD stage 3a had improvement of their serum creatinine level and GFR. In the group of patients with CKD stage 3b, 66.7% had improvement of parameters of renal function test and downstaging of CKD. Fetal precursor cell application in management of CKD is a promising therapeutic modality and requires further detailed analysis and continued clinical trials.

Key words: Kidney, renal failure, precursor stem cell, xenotransplantation, kidney repair.

INTRODUCTION

Chronic kidney disease (CKD) is characterized by progressive deterioration of renal function due to loss of functioning nephrons. The main causes of CKD are hypertension, diabetes mellitus, nephrolithiasis, recurrent infections of urinary tract, various autoimmune disorders, etc. In spite of tremendous achievements of modern medical science, CKD is still considered as irreversible, gradually worsening condition that ultimately results in end-stage renal failure (ESRF), which subsequently dooms patients for regular hemodialysis and kidney transplant. Hemodialysis is associated with high morbidity rate, high cost of the procedure and life-long post-operative management and follow-up (El Nahas and Bello, 2005).

Such situation urges to seek for new advanced therapeutic modalities that are able to restore renal function or at least significantly slow down the progression of CKD. Recent research and studies has shown that the most promising opportunity to restore

nephron functionality is stem cell therapy (Hopkins et al., 2009; Benigni et al., 2010; Gilbert et al., 2012; Li and Wingert, 2013).

Adult human kidney is comprised of hundreds of thousands to nearly one million of nephrons. It contains different types of cells including glomerular podocytes, tubular epithelial cells, endothelial cells, pericytes, interstitial fibroblasts, and dendritic cells (Martin and Parkhurst, 2004; Romagnani, 2011; Romagnani et al., 2013). During lifetime, various kidney cells exhibit different turnover; however in overall, the cell turnover in kidney is remarkably lower than in other organs (Ronconi et al., 2009a, b; Smeets et al., 2013; Liu, 2011).

As a result to acute and chronic damages, such as inflammation, ischemia, autoimmune processes kidney launched various mechanisms of regeneration, including compensatory renal hypertrophy, cell proliferation, reprogramming of endogenous renal cell, renal progenitor cell differentiation, mesangial cell proliferation and

migration, migration of bone-marrow cells into kidney, and neoangiogenesis (Liu, 2011; Choudhury and Levi, 2011). Some cells, like mesenchymal cells, have ability to differentiate into epithelial cells, and some renal epithelial cells have ability to dedifferentiate in order to further proliferate, migrate and differentiate into necessary type of cells (Lazzeri et al., 2007; Ezquer et al., 2012; Fleig and Humphreys, 2014; Maeshima et al., 2006). However, after renal organogenesis is completed by 36-38th week of gestation, there is no more universal renal progenitor stem cell pool left in the kidney (Aggarwal et al., 2013; Sagrinati et al., 2006). Such limited regeneration potential of the kidney leaves no other choice to tackle progressing renal failure but using stem cells (Romagnani and Remuzzi, 2013).

The objectives of this article were to evaluate the existing data on the stem cell application in management of CKD and to assess the potentials of the fetal precursor stem cell therapy in alleviating the degree of renal failure.

LITERATURE REVIEW

Variants of stem cell therapy

Currently there are few options of stem cells available: bone marrow-derived cells (BMDCs), embryonic stem (ES) cells, autologous adipose-derived mesenchymal stem cells (ADMSCs), induced pluripotent stem (iPS) cells, and renal progenitor cells.

Adipose-derived mesenchymal stem cells (ADMSCs) have the capacity to differentiate into fat, bone, cartilage and muscle cells. ADMSCs are easily accessible for harvesting and culturing in high volume and possess anti-inflammatory and immunomodulating functions (D'Addio et al., 2014; Ni et al., 2015). However, its benefit is confined to suppression of inflammatory process. There is no data supporting that ADMSCs can differentiate into any renal cell. Hence, there is no significant role of ADMSCs either in downstaging the renal failure or in slowing down its progression.

The most widely used stem cells in renal failure are Bone Marrow-derived Mesenchymal stem cells (MSCs). The existing scientific evidences on efficacy of MSCs in renal failure are controversial (Ezquer et al., 2008, 2009; Reinders et al., 2013; Volarevic et al., 2011; Chamberlain et al., 2007; Zhang and Zhao, 2014). Some studies report the effect of MSCs in preventing the renal fibrosis, though that was mostly due to protection from further injury, rather than due to regeneration of the damaged renal parenchyma (Lv et al., 2014; Ezquer et al., 2015). Other studies have shown absence of clinical response to MSCs transplantation (Liu, 2011; Leuning et al., 2014; Herrera and Mirotso, 2014). In spite of existing data on some potential benefits of MSCs in managing the renal failure, the bottom line is still the same – MSCs have minimal nephrogenic differentiation potential.

Embryonic stem cells (ESC) are the pluripotent stem cells derived from the inner cell mass of a blastocyst. Theoretically these cells have potential to be used in regenerative therapy of any organ or tissue. Few experiments demonstrated that ES cells can differentiate into renal epithelial cells and once introduced directly into developing metanephros can differentiate into tubular epithelia with nearly absolute efficiency (Lam and Bonventre, 2015; Couri and Voltarelli, 2009; Roche et al., 2006; Chou et al., 2014). However multiple studies confirmed that implantation of ES cells leads to the formation of differentiated tumors comprising all three germ layers, resembling spontaneous human teratomas. According to the study of Yamamoto et al. (2006), ES cells can develop teratoma within 14 to 28 days after transplantation (Hannes et al., 2009).

Discoveries that were made by Takahashi and Yamanaka (2006) in the field of cell transdifferentiation have opened new possibilities of using induced pluripotent stem cells (iPSCs) for kidney regeneration. iPS cells were initially discovered by reprogramming human fibroblasts to become pluripotent stem cells by combined overexpression of four specific transcription factors - Oct4, Sox2, Klf4, and c-Myc, introduced via retroviral delivery (Kobayashi et al., 2008; Hayashi, 2006).

However iPSCs also have limitations: not all adult cells can be similarly reprogrammed; the delivery of undifferentiated iPSCs back into a patient also carries the risk of teratoma formation; oncogenic risks, as Klf4 and c-Myc are oncogenic factors; cells differentiated from iPS cells can induce T-cell dependent immune response (Herrera and Mirotso, 2014; Lam and Bonventre, 2015; Kobayashi et al., 2008; Hayashi, 2006).

Stem cell xenotransplantation

Stem cell xenotransplantation (SCX) – is transplantation of stem cells from one species to another. The core benefit of the SCX – is accessibility of organ-specific precursor cells, - fetal cells that have lost their totipotency and pluripotency, however they maintain the multipotency or oligopotency – ability to differentiate into few cell types within one germ layer.

Precursor stem cells are obtained from the organs of animal fetuses in the final stage of their antenatal development (Hayashi, 2006; Goligorsky, 2014; Li and Ikehara, 2014). Various species of animals are used. Xenotransplantation is studied all over the World, and recently Japan started pig-derived cells implantation in type 1 diabetes patients. However, in our opinion, the most preferable sources of fetal cellular material are sheep and rabbits. Sheep and rabbits are resistant to lots of diseases, are easy and convenient in maintaining the colony, and there are no cultural and religious taboos associated with these animals (Yang and Cheng, 2013;

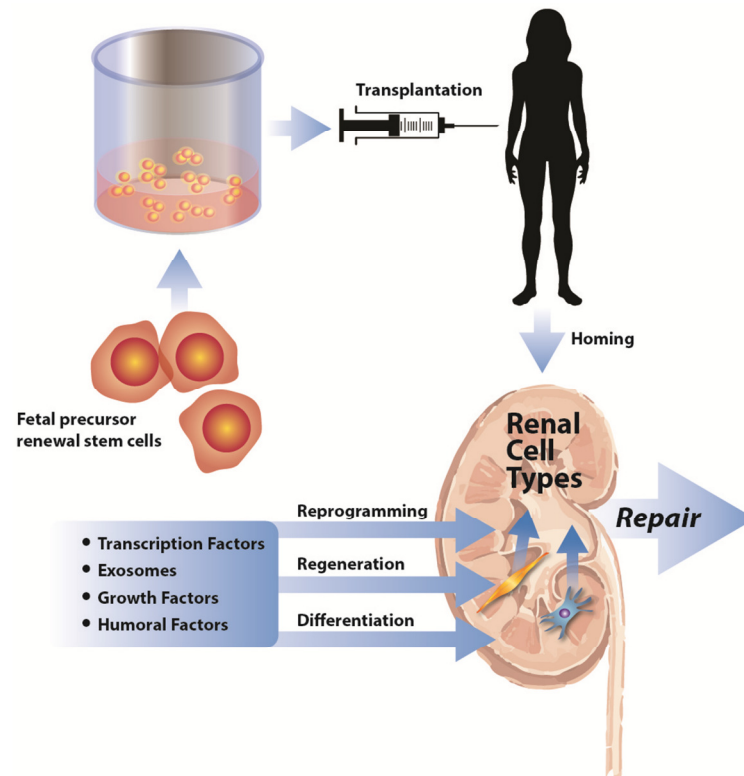


Figure 1. Principles and mechanisms of live precursor cell therapy are based on “homing effect” and paracrine effect. Paracrine effect promotes reprogramming, regeneration and differentiation of the kidney.

Yamashita et al., 2005; Lee et al., 2010; Solomon, 1977; Messier and Leblond, 1960; Hartman et al., 2007).

Animal-donors used for preparation of stem cells are originated from “closed” colony – a documented lineage for over 30 generations bred in facility not exposed to outside environment. The closed colonies are established according to international standards and regular surveillance programs, and constant monitoring is conducted.

Speed, efficiency and strict aseptic and temperature conditions are prioritized during the process of procurement, preparation, manufacturing, as well as storage, and transportation.

Principles of precursor cell therapy

The mechanisms of live precursor cell therapy are based on “targeting” the specific organ (“homing effect”) and replacement of impaired cell pool and activation/stimulation of the specific cellular factors inducing the tissue repair in the recipient’s organism. Most of the studies and publications claim that implanted cells disappear from the implantation site and with radionuclide analysis are identified within 48-72 h in the target-organ or tissue, following the principle of the

organospecificity (Figure 1; Solomon, 1977; Messier and Leblond, 1960; Schmid and Stein, 1967).

Some of the cells, after been implanted, are taken by phagocytes with subsequent release of active cellular materials. Such mechanism of action of SCX is based on paracrine interaction with resident cells, by release of growth and anti-inflammatory factors, cytokines, prostaglandins, exosomes, vascular endothelial growth factor, insulin-like growth factor etc., causing a biological effect. Such mechanisms also explain the clinical efficiency (although at a lower degree compared to precursor cell therapy) of the organ-specific cell extracts, which has almost a century-long history of successful application in Europe. Within 5 h after implantation, the radioactively-tagged injected materials are showing its distribution. Usually, significant clinical effect and changes in objective parameters can be seen at least after 3-4 weeks after implantation (Hayashi, 2006; Yamashita et al., 2005).

Among the great benefits of fetal precursor cell xenotransplantation are the availability of more than one type of cells and unlimited amount of cells available for implantation. From the decades of world-wide experience of precursor cell xenotransplantation, chronic glomerular defects respond to the therapy quite well (Yamashita et al., 2005; Solomon, 1977). The core of treatment protocol

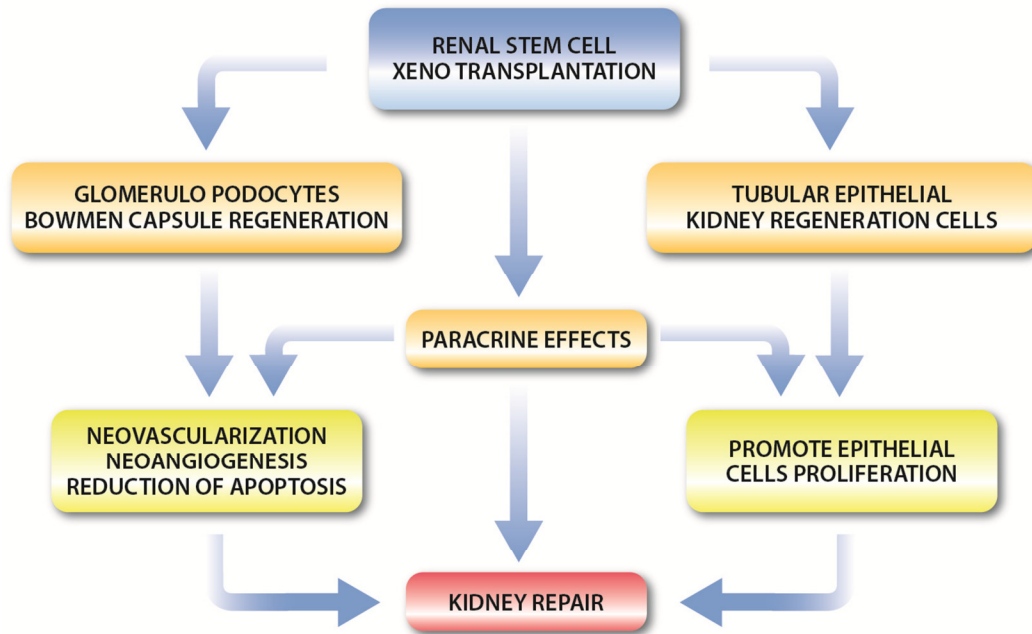


Figure 2. Pathways of kidney regeneration after precursor cell implantation. Kidney regenerates through tubular epithelial cells and glomerulopodocytes regeneration, as well as via paracrine effects.

is kidney precursor cell. However, stem cells from other organs able to facilitate better clinical effect should be used as well. It is advisable to add precursor cells from adrenal cortex, mesenchyme, vascular endothelium, and placenta. The later will provide a wide range of various growth factors and cytokines stimulating the paracrine reactions in repairing kidney (Figure 2; Schmid and Stein, 1967; Molnar, 2006).

Depending on every patient's condition, therapeutic prescriptions are individualized. In the case of autoimmune disease precursor cells from thymus, spleen can be additionally prescribed, in case of diabetes mellitus – the diabetic protocol should be added (Schmid and Stein, 1967; Molnar, 2006).

Generally fetal precursor cell therapy is compatible with any other concomitant treatment. Despite of that, to eliminate potential damage to the implanted cells, we still suggest to avoid administration of other drugs within 48-72 h before and after implantation (Molnar, 2006).

Usually implantations are well tolerated by patients and the immediate response depends on patient's condition. Starting from next day after injection, patients may experience some fatigue and transitory low-grade fever. It is recommended to have few days of rest, avoid physical exercise and certain activities, like sun bathes, sauna, spa, heavy outdoor activities, stop the consumption of alcohol, smoking and avoid vaccinations for the following one month (Molnar, 2006).

Contraindications for precursor cell therapy are: recent or ongoing infection, vaccination within one month prior to implantation, acute medical conditions (i.e. myocardial

infarction, stroke), regular consumption of cytostatic medications or current administration of chemotherapeutic agents, radiotherapy (Schmid and Stein, 1967; Molnar, 2006).

To evaluate and systematize results of the fetal precursor cell therapy is an extremely challenging task. Mainly it is because of individual approach applied in every case, difficulty to standardize treatment protocols and prescriptions, as well as cost of the treatment. Most of the patients are dispersed geographically and contact with their respective primary care doctors or medical institutions they are attached to, that does not make medical data and results of treatment obtained easily for purposes of systematic analysis.

MATERIALS AND METHODS OF THE COHORT STUDY

We have collected clinical data on 23 patients with diabetic nephropathy who received fetal precursor cells. The cohort was multi-centric. Patients varied in their ethnicity, age and co-morbid. The main inclusion criteria were CKD stage 3a and 3b. Stage of renal failure was determined according to GFR values: 14 patients had 3a stage (GFR ranged 45-59 mls/min/1.73m²) and 9 patients – 3b stage (GFR ranged 30-44 mls/min/1.73m²). CKD stage 3a group consisted of 9 males and 5 females in the age 39-62 years (mean age 44.2). Group of patients with CKD stage 3b consisted of 5 males and 4 females in the age from 37 to 64 years old (mean age 54.8). Male

Table 1. Changes of mean GFR levels in observed groups. Comparison before the implantation, after 6 months and after 1 year ($p < 0.5$).

Mean GFR (mls/min/1.73m ²)	CKD stage 3a (n=14)		CKD stage 3b (n=9)	
	Male (n=9)	Female (n=5)	Male (n=5)	Female (n=4)
Day 0	52	43	39	38
6 months	54	47	41	40
1 year	57	49	42	41

patients in the CKD stage 3a group had mean serum creatinine level $132.44 \pm 0.32 \mu\text{mol/l}$, GFR – 52 mls/min/1.73m²; females - $121 \pm 0.02 \mu\text{mol/l}$ and 43 mls/min/1.73m². In the group of patients with CKD stage 3b mean serum creatinine level in males was $169.8 \pm 0.01 \mu\text{mol/l}$; mean GFR - 39 mls/min/1.73m² and in female subgroup – $135.5 \mu\text{mol/l}$ and 38 mls/min/1.73m² respectively.

Prior to implantation, all patients signed an informed consent and went through a thorough clinical and biochemical examination to find possible contraindications to procedure and to document the base-line renal profile. The standard prescription of stem cells contained combination of precursor cells from kidney; a mixture of precursor glomerular podocytes and precursor tubular epithelial cells, precursors of hepatocytes, β -cells of pancreas, mesenchymal, vascular endothelial cells, cardiac myocytes, stomach and intestinal mucosa cells, bone marrow cells.

After precursor cell implantation during follow-up and subsequent maintenance treatment, patients received organ specific peptides (cellular extracts from kidneys, pancreas, liver, heart, and mesenchyme). The response to cell therapy was evaluated 6 months and 1 year after the initial implantation.

RESULTS

In the post-implantation period, majority of patients noted improvements in their general medical condition. Two patients with CKD stage 3a had insignificant clinical improvement and their GFR remained at the initial level. One patient had serum creatinine level slightly increased (from 143 to 144 $\mu\text{mol/l}$). In 11 patients the progress was noted: their general condition has improved dramatically, GFR level has substantially changed, mean serum creatinine levels reduced to $128 \pm 0.02 \mu\text{mol/l}$ and GFR reached 54 mls/min/1.73m² in males, and serum creatinine $113 \pm 0.2 \mu\text{mol/l}$ and GFR 47 mls/min/1.73m² in female subgroup. Hence 78.5% of patients with CKD 3a had significant improvement and down-staging of CKD.

In the group of patients with CKD stage 3b, 6 people demonstrated reduction of GFR levels (66.7%). In male subgroup of patients with CKD stage 3b, mean creatinine levels reduced to 161.7 $\mu\text{mol/l}$ and mean GFR became

41 mls/min/1.73m²; in female subgroup – 129 $\mu\text{mol/l}$ and 40 mls/min/1.73m² (Table 1).

Results obtained 1 year after the initial implantation proved a strong lasting effect of precursor cell xenotransplantation. None of the patients had their renal function deteriorating, and serum creatinine levels and GFR in most of the patients showed continuous tendency for improvement (Figure 3).

There were no allergies, adverse reactions or any complications observed in treated patients. Most of the patients underwent repeated sessions of cellular therapy, results of which will be reported in further publications.

DISCUSSION

The review of the literature data on the existing modalities of stem cell therapy in CKD clearly indicates the extreme challenge in achieving any significant improvement in renal function. Application of ESC and iPSC cannot be widely used yet due to its highly probable teratoma formation and even malignant potential. Various types of mesenchymal stem cells derived from different sources are proven to bring certain benefit in CKD patients; however they fail to produce improvement in GFR levels and down-staging of CKD stage.

There is no doubt that fetal precursor stem cells derived from the partially differentiated kidney at the final stages of embryogenesis are the most safe and reliable source of replacement cellular pool. There is no possibility from the legal, ethical and medical point of view to get sufficient supply of human renal precursor stem cells. This opens a unique opportunity for the usage of xenogeneic fetal precursor stem cells. Xenogeneic cellular therapy was proven safe over many decades of successful application in Europe. Latest advances in approval of mass usage of animal stem cell implants for the management of diabetes in Japan has pushed the boundaries of cellular therapy and opened ways for future organ regeneration technologies.

Presented cohort study is giving the inside view on potentials of kidney regeneration. Fetal precursor cell xenotransplantation allowed achieving significant reduction of chronic renal failure stage in almost three quarters of the patients. The provided treatment has also demonstrated a good stability, as within a year there

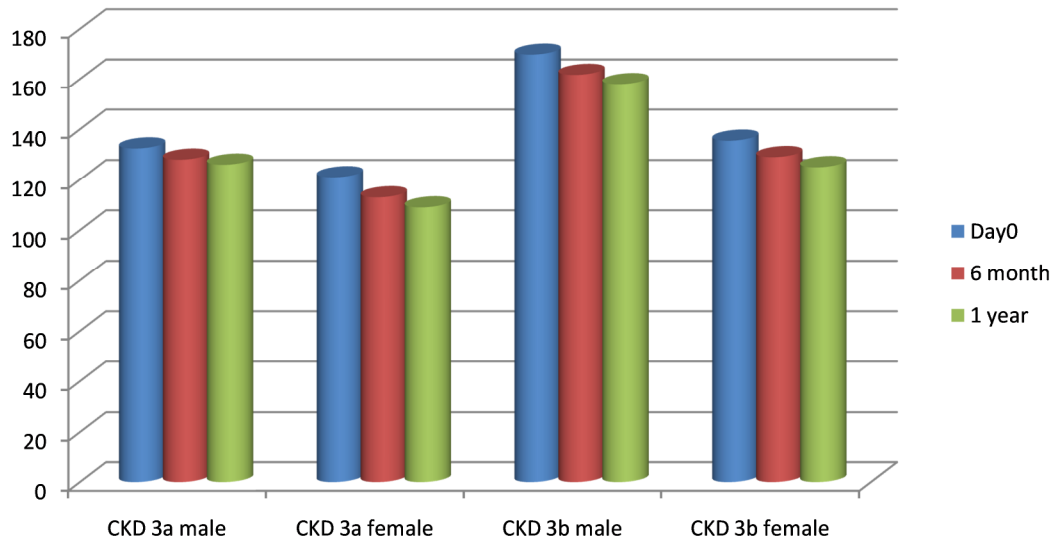


Figure 3. Dynamics of mean serum creatinine level in observed patients with CKD.

were no adverse outcomes noted. In our future reports we will update on the progress of the research and will provide more valid data.

Conclusion

In conclusion, complexity of the kidney's structure makes its reparation and regeneration an extremely challenging task and defies difficulties in managements of CKD. In spite of the variety of different types of stem cells available in today's world, fetal precursor stem cells appear to be the most promising option of slowing down and even reversing the renal failure. Stem cell xenotransplantation deserves more attention of scientists and researchers and requires further studies and development.

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