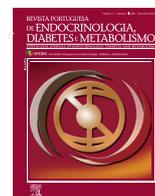




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Artigo Original

Simultaneous Pancreas-Kidney Transplantation: 15 Years Experience from a Single Center in Portugal



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A B S T R A C T

Introduction: Pancreas transplantation alone or associated to renal transplantation appears as the most efficient method to restore euglycemia in a person with type 1 diabetes. This study aimed to characterize patients undergoing simultaneous pancreas-kidney transplantation (SPKT) in Centro Hospitalar do Porto (CHP), a single centre in Portugal, and analyse its evolution.

Methods: We retrospectively evaluated all pancreas-kidney transplants performed between May 2000 and May 2015 concerning several variables.

Results: There were 180 transplants (51.1% females); the patients mean age at the time of transplantation was 34.8 ± 6.0 years; the mean time from diabetes diagnosis was 23.7 ± 6.0 years; the mean duration of dialysis was 27 ± 21.1 months; the mean inpatient time at transplantation procedure was 24 ± 18.6 days. Sixteen patients died. Among survivors, the loss of pancreatic and kidney grafts occurred in 39 and 20 patients respectively. Survival rates (death-censored) at 1, 5, 10 and 15 years were, respectively, 97%, 95%, 90% and 76% for patients, 96%, 93%, 84% and 79% for renal allograft and 87%, 80%, 74% and 71% for pancreatic graft.

Discussion: With the results of our simultaneous pancreas-kidney transplantation program, we conclude that this procedure remains a very valid option to treat selected people with type 1 diabetes mellitus.

Transplante Reno-Pancreático: 15 Anos de Experiência de um Único Centro em Portugal

R E S U M O

Introdução: O transplante de pâncreas total associado ou não ao transplante renal surge como o método mais eficiente para restabelecer a euglicemia na pessoa com diabetes tipo 1. Este trabalho teve como objectivo caracterizar os doentes submetidos a transplante simultâneo rim-pâncreas no Centro Hospitalar do Porto e analisar a sua evolução.

Metodologia: Foram avaliados retrospectivamente todos os transplantes reno-pancreáticos realizados entre Maio/2000 e Maio/2015 em relação a diversas variáveis clínicas e laboratoriais.

Resultados: Foram realizados 180 transplantes (51,1% doentes do sexo feminino); a idade média dos doentes no momento do transplante foi de $34,8 \pm 6,0$ anos; o tempo médio de diagnóstico de diabetes foi de $23,7 \pm 6,0$ anos; a duração média do período de diálise foi de $27 \pm 21,1$ meses; o tempo de internamento médio para o procedimento foi de $24 \pm 18,6$ dias. Dezanove doentes morreram. Entre os sobreviventes até à data de conclusão do estudo, 20 doentes tinham perdido o enxerto renal e 39 o enxerto pancreático. As taxas de sobrevivência a 1, 5, 10 e 15 anos foram, respectivamente, 97%, 95%, 90% e 76% para os doentes, 96%, 93%, 84% e 79% para o enxerto renal e 87%, 80%, 74% e 71% para o enxerto pancreático.

Discussão: O sucesso do transplante reno-pancreático determinado por taxas de sobrevida dos doentes

Palavras-chave:

Análise de Sobrevida

Diabetes Mellitus Tipo 1

Transplante de Pâncreas

Transplante de Rim

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e dos enxertos semelhantes aos dados internacionais permitem-nos concluir que este procedimento se mantém como uma opção muito válida no tratamento de pessoas com diabetes *mellitus* tipo 1 bem selecionadas.

Introduction

The discovery of insulin in 1921 has saved the lives to millions of patients with type 1 diabetes mellitus and the new insulin analogues allow a more physiological treatment slightly more close to the endogenous insulin secretion pattern. Nevertheless this did not mean the cure. Diabetic patients develop health problems more frequently than healthy people and diabetes remains a major cause of morbidity and mortality.¹ The Diabetes Control and Complication Trial and its follow-up study (DCCT/EDIC) demonstrated that intensive therapy resulted in decreased rates of retinopathy, nephropathy, neuropathy and cardiovascular events in type 1 diabetic patients.² However, intensive insulin therapy in the real world has an elevated success rate only if there is a sustained compliance and commitment, and is frequently restricted by the risk of hypoglycemia. For these reasons many efforts have been made to find the ideal treatment for these patients. In the 60s the study of pancreas and islet cell transplantation emerged as a new solution for diabetes.³ Islet cell transplantation is a minimally invasive and low morbidity procedure, but rates of long-term success are also low and is still an experimental technique under development.⁴ On the other hand, whole pancreas transplantation has shown good results and is still the best option for replacing the endocrine function of the pancreas and the therapeutic modality that is closest to the cure.³ Successful transplantation reflects on the insulin injections freedom as well as from frequent blood sugar self monitoring, risk of hypoglycemia, stopping or possibly to delay the progression of the complications of diabetes.⁵ Several studies have shown that the posttransplant improvement in glucose metabolism is maintained for many years.⁶ Pancreas transplantation requires lifelong immunosuppression to prevent graft rejection and recurrence of the autoimmune process. Taking into account the risks of surgery and immunosuppressive treatment, the American Diabetes Association (ADA) recommend pancreas transplantation in diabetic patients with end stage renal disease who have had or plan to have a kidney transplant.⁷ Indications for isolated pancreatic transplant are restricted to patients without substantial renal disease with consistent failure of insulin-based management to prevent acute complications manifested by history of frequent ketoacidosis or hypoglycemic coma or incapacitating clinical and emotional problems with exogenous insulin therapy.⁷ SPKT is the modality most often used and with the best results of pancreatic graft survival when compared to other pancreas transplant modalities such as pancreas after kidney (PAK) or pancreas transplantation alone (PTA).⁸ However, patient and graft loss after SPKT is higher than in kidney transplantation alone in the early phase after surgery.^{8,9} Regardless of the immediate results, at 1 year and especially in the long-term, patient and kidney graft survival rates are generally comparable with those seen with living-donor kidney allografts alone and superior to those observed after deceased-donor kidney allografts alone.⁹ Moreover outcomes of SKPT have improved in the last decades and SPKT is currently considered the best treatment for type 1 diabetes patients with chronic renal failure, allowing, when successful, a significant improvement on quality of life.⁸⁻¹⁰

In 1998, at Centro Hospitalar do Porto (CHP) was initiated a unique program of simultaneous pancreas-kidney transplant in

Portugal with the first transplant performed in 2000.¹¹ The aim of this study was to analyze the program outcomes since its beginning.

Methods

The first SPKT fulfilled in the CHP transplant unit was performed in May 2000. In our program, the pre-transplant evaluation is conducted by the Nephrology department and comprises an initial assessment by all specialties involved in the unit. The selection criteria are patients with type 1 diabetes and impaired chronic renal function requiring renal replacement therapy. The selection of candidates for SPKT is far more complex and comprehensive than for the transplantations of isolated kidney, due to the type of patients, with important comorbidities, namely vascular disease. Major exclusion criteria are other type of diabetes than type 1, older than 50 years, and significative cardiovascular, cerebrovascular or peripheral vascular disease not soluble prior to transplantation; other exclusion criteria are common to other transplants - not controlled psychiatric illness, drug addiction, active cancer or infection disease and history of lack of adherence to treatment; the stage of retinopathy and sensorimotor and autonomic neuropathy are minor criteria. Patients that met the inclusion criteria and have no exclusion criteria are placed on a waiting list for transplantation. All transplants are performed with grafts obtained from deceased donors (both grafts from the same donor). Donors are deceased patients under 50 years who do not have exclusion criteria, which includes obesity, alcohol abuse, abdominal trauma, use of pressor amines in high doses (cold ischemia), macroscopic alterations that contraindicate the organs harvesting (example: lush fat involving the pancreas). All transplants require ABO compatibility and negative crossmatch with the donor. It is intended to transplant with the greatest number possible of HLA compatibilities (for loci A, B and DR), but many transplants are performed without any HLA compatibility. The number of available organs is so small that we can not waste them. The immunosuppression protocol used in this type of transplant (with lymphocyte depleting antibodies) allows us to do so. Regarding the kidney transplant it seems that minimizing HLA mismatches increases organ survival but with regard to the pancreas as far as one knows, there is no evidence that HLA matching is associated with improved pancreas survival.¹² The immunosuppressive protocol is the one most commonly used for SPKT around the world, namely anti-thymocytic globulin, tacrolimus, corticosteroids and mycophenolate mofetil. After the sixth month, the unit policy is to progressively taper steroids to complete withdrawal whenever possible. In terms of surgical technique it is first made the pancreas transplantation in the right iliac fossa using whole pancreas with duodenal bow, using a duodenal-jejunal anastomosis, with enteric drainage of exocrine secretions and systemic vascular anastomosis to the iliac vessels. Then it is done the kidney transplant from the same donor in the left iliac fossa, anastomoses the iliac vessels and urological surgery by the usual renal transplant technique. There was a modification in the vascular technique over the years: during the first years the arterial supply to the pancreas graft was provided by an arterial reconstruction; since 2005 it is used a aortic patch with the entire arterial supply to the pancreas graft directly anastomosed to

the recipient common iliac artery, with no further arterial reconstruction. This resulted in a lower incidence of surgical complications. More detailed aspects of this program and the first 10 years results are published elsewhere.¹¹

The aim of this study was to analyze the program outcomes since its beginning. To do so we conducted a retrospective evaluation of all patients undergoing a pancreas-kidney transplant, performed between May 2000 and May 2015 in CHP transplant unit, with a minimum of 3 months of follow-up. The results are presented as mean \pm standard deviation for continuous variables with normal distribution and as percentages for categorical variables. The survival of patients was determined from the date of transplantation until death. Pancreatic graft was considered functioning while the receiver remained insulin-independent. The kidney graft was considered functioning while the receiver remain dialysis-free. The death of the receiver with a functioning graft was considered graft failure. Survival curves were calculated using Kaplan-Meier method.

Results

Since the first transplant in May 2000, 180 SKPT were performed in CHP. The number of transplants increased each year until 2009 (19 transplants) and stabilized since then at about 14 transplants per year. These 180 patients, 92 women and 88 men, had a mean age of 34.8 ± 6.0 years at the time of transplantation and a mean duration of diabetes of 23.7 ± 6.0 years.

The mean pretransplant fasting glucose and HbA1c was 232 ± 139 mg/dL and $8.5\% \pm 1.6\%$, respectively. The mean insulin daily dose was 39 ± 12 units to a mean pre-transplantation weight and body mass index of 60.0 ± 9.3 kg and 22.4 ± 2.6 kg/m² respectively. About 14% were overweight or obese. Eight patients received a pre-emptive transplantation; the mean period of dialysis treatment of the remaining was 27 ± 21.1 months and the mean creatinine value was 7.1 ± 5.0 mg/dL. The mean age of the deceased donor was 28.2 ± 10.5 years. The mean inpatient time was 24 ± 18.6 days (median time of 19 days) including an average of 3.6 ± 10.3 days (median 2 days) in the intensive care unit. Forty four patients (24.4%) required surgical reintervention. The initial cause was infection (fifteen cases), hemorrhage (fourteen cases), thrombosis (eleven cases), intestinal obstruction (two cases) and urine leakage (two cases). Sixteen patients died, 6 of which in the first year post-transplant. The median time to death was 3.9 years. Two of these patients had both functioning grafts. Early deaths (< 12 months) were due to infection (five cases) and unclear cause (one case); late deaths were caused by myocardial infarction (four cases), stroke (one case), infection (two cases), malignancy (one case of lung cancer), hypoglycemia (one patient with pancreatic graft loss) and uncontrollable gastrointestinal bleeding (one case). In conclusion, infection was the leading cause of death (seven cases) mainly in the early period, followed by cardiovascular or cerebrovascular disease (five cases), these mainly in the late follow-up.

The loss of pancreatic grafts occurred in 46 patients (25.6%).

Table 1. Causes of patient death and graft failure

Occurrence	Timing of occurrence	Main cause
Pancreas loss (n=46)	Early loss (n = 21; 45.7%)	Thrombosis (n = 10) Rejection (n = 1) Infection (n = 7) Unknown (n = 1) Haemorrhage (n = 2)
	Late* loss (n = 25; 54.3%) *(> 6 months follow-up)	Thrombosis (n = 2) Rejection (n = 9) Infection (n = 2) Death with functioning graft (n = 7) Unknown (n = 4) Haemorrhage (n = 1)
Kidney loss (n=26)	Early loss (n = 8; 30.8%)	Death with functioning graft (n = 2) Thrombosis (n = 4) Infection (n = 2)
	Late* loss (n = 18; 69.2%) *(> 6 months follow-up)	Rejection (n = 13) Death with functioning graft (n = 4) Unknown (n = 1)
Patient death (n=16)	Early death (n = 6; 37.5%)	Infection (n = 5) Unknown (n = 1)
	Late* death (n = 10; 62.5%) *(> 12 months follow-up)	Myocardial infarction (n = 4) Stroke (n = 1) Infection (n = 2) Malignancy (n = 1) Hypoglycemia (n = 1) Digestive haemorrhage (n = 1)

The causes were thrombosis (twelve cases), rejection (ten cases), infection (nine cases), death with a functioning graft (seven cases), unclear cause (five cases) and hemorrhage (three cases). Excluding death with a functioning graft, the median time to pancreas graft loss was 0.2 years post-transplantation. Seven patients with pancreatic graft loss were retransplanted with a new pancreas, one graft remains functioning. The loss of renal graft occurred in 27 patients (15%). Causes were rejection (thirteen cases), death with a functioning graft (seven cases), thrombosis (four cases), infection (two cases) and unclear cause (one case). Excluding death with a functioning graft, the median time to kidney graft loss was 3.7 years post-transplantation. Table 1 summarizes the causes of graft failure and patient death.

At August 2015, 164 patients (91.1%) were alive, with a mean age of 41.32 ± 6.1 years; 154 (85.6%) maintained a functioning renal graft, 134 (74.4%) maintained a functioning pancreatic graft and 130 patients (72.2%) have both functioning grafts. Among patients with functioning kidney graft, mean serum creatinine was 1.24 ± 0.44 mg/dL and creatinine clearance estimated by the MDRD formula was 65.5 ± 20.8 mL/min/1.73m². Patients with functioning pancreatic graft had a mean fasting glucose, HbA1c and peptide-C of 84.2 ± 14.1 mg/dL, $5.3\% \pm 0.5\%$ and 2.9 ± 1.8 ng/mL, respectively.

Survival rates (death-censored) at 1, 5, 10 and 15 years were, respectively, 97%, 95%, 90% and 76% for patients, 96%, 93%, 84% and 79% for renal allograft and 87%, 80%, 74% and 71% for pancreatic graft (Fig. 1).

Discussion

The first pancreas transplant was performed in 1966 in Minnesota, but the initial rates of graft and patient survival were low. Very few procedures were performed in the years after and it was considered an experimental technique until 1990. The subsequent introduction of better immunosuppressive regimens, new surgical techniques, the increased knowledge about managing complications and the selection of healthier recipients resulted in markedly improved outcomes.^{8,9} Due to perioperative complications, SPKT is associated with increased risk of perioperative mortality and

greater morbidity when compared with kidney transplant alone. This facts were reflected by longer initial hospital stay and more frequent rehospitalization during the first year posttransplant.⁸⁻¹⁰

In CHP the patients survival rates are similar to those reported by International Pancreatic Transplant Registry (IPTR): 95 to 98 percent at one year, 78 to 88 percent at five years and over 70% at 10 years post-operatively.^{8,13} The causes of death were similar to those reported in the literature: surgery related complications such as infection in the first year post-transplant and cardiovascular/cerebrovascular disease as the main cause of late deaths.^{8,9} The major causes of graft loss are thrombosis and infection in the short term and immunologic rejection in the long term.^{8,9} Acute rejection is 1.5 to 2 times more common and more likely to be recurrent in SPKT than in kidney transplantation alone recipients and the more aggressive immunosuppressive strategies used exposes the patient to an increased risk of bacterial, fungal, and viral infections.^{14,15}

Regarding to pancreas graft loss the majority occur in the early post-operative period related to technical failures (thrombosis, leaks, bleeding, infection, pancreatitis).^{8,9} Some frequent complications were greatly reduced with the alteration from bladder exocrine drainage to enteric drainage of the pancreas graft.¹⁶ The IPTR results reported pancreas graft survival rates for SPKT procedures of 86 percent at 1 year and 54 percent at 10 years.⁸ The results in CHP were similar to those described with the majority of pancreatic losses occurring in the early phase and the main causes being thrombosis, infection and rejection. It is important to considerer that among pancreas recipients, those who receive SPKT have better graft survival than pancreas transplantation alone.¹⁷ The renal graft seems to work as a sentinel organ giving earlier signs in acute rejection, helping to monitor the pancreas graft.¹⁷ Therefore measurements of serum creatinine are used to monitor for possible acute rejection of both grafts in patients with a functioning renal allograft.¹⁶

Regarding to kidney, graft loss in our center occurred in the late period in the majority of patients and rejection was the main cause, as reported by other series.^{9,10} Kidney allograft survival rates among recipients of SPKT are superior to those observed after deceased-donor kidney allografts alone.¹⁸ The restoration

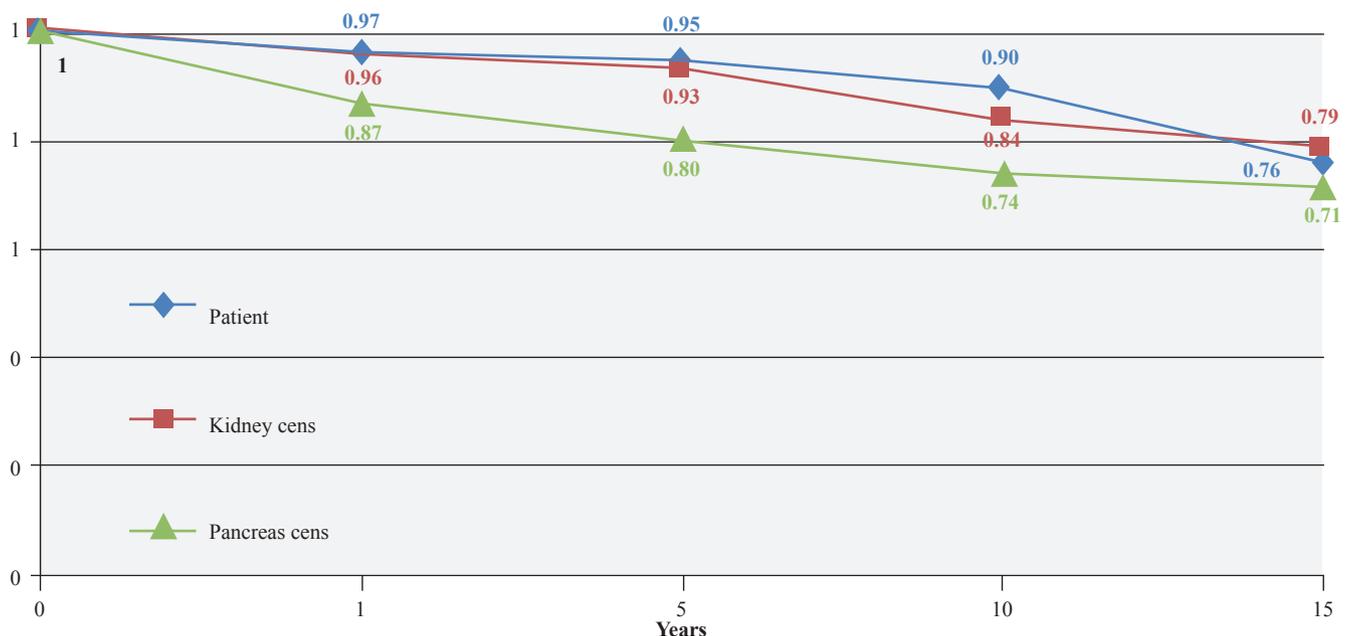


Figure 1. Patient and graft survival rates of the 180 SPKT (pancreas and kidney data censored for patient death with a functioning graft)

of endogenous gluco-regulatory mechanism protects the kidney graft of hyperglycemia, preventing the recurrence of nephropathy and improving kidney survival.^{18,19}

The major benefit of combined kidney-pancreas transplantation is an improved quality of life – as we also documented in a recent publication²⁰ due to freedom from insulin injections, frequent finger pricks, hypoglycemia and dialysis. Even in cases with pancreatic graft failure our experience shows that some patients are more able to control diabetes after transplant, presenting smaller insulin needs, less glycemic variability and less hypoglycaemia. The other established benefit are the improvement of nephropathy - some studies have shown that native renal structure presents diminished mesangial mass after 10 years- and the prevention of recurrent diabetic nephropathy in the transplanted kidney.^{19,20} Multiple studies have been performed on the effects of pancreas transplantation on the secondary complications of diabetes. However most of these were performed with small numbers of patients. Most studies report that normalization of glucose may benefit the long-term micro and macrovascular diabetic complications.²¹⁻²⁵ For example, the velocity of motor and sensory nerve conduction as well as clinical neuropathy seems to stabilize.^{21,22} However effects on diabetic retinopathy remain controversial.^{23,24} There may be also some benefit on the macrovascular disease which seems to remain stable after successful pancreas transplant when compared with continuous deterioration in patients with failed pancreas transplant.²⁵ The diabetic foot deserves special consideration. Some procedures related with the transplantation of both grafts may carry more propensity to diabetic foot injury, and further risk of lower limb amputation. The therapy with corticosteroids may be associated with the development of de novo Charcot osteoarthropathy.^{26,27} Some cases with a Charcot-modified clinical presentation during the postoperative convalescence period after SPKT have been described.²⁶ The immunosuppressive agents, obligatory for the prevention of organ rejection, lead to an increased risk of severe infections, namely foot ulcers. Another point of concern is the eventual compromise of circulation by diverting blood from the iliac vessels of the lower limbs to the grafts; however studies have shown that transplanted grafts to iliac arteries does not significantly deteriorate ischemia in adults with lower extremity peripheral arterial disease.^{28,29} Despite the previously mentioned, most studies show decreased incidence of diabetic ulcers and amputation, which may be related to some benefit in improvement of microcirculation.^{30,31} More studies, especially randomized controlled studies are necessary to clarify the effect of SPKT on secondary complications of diabetes.

With the success of the reno-pancreatic transplantation determined by good survival rates of patients and grafts and the improvement in quality of life we conclude that this technique stands out as a very valuable option to treat selected patients with type 1 DM.

Responsabilidades Éticas

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

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Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos

estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial.

Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação dos dados de doentes

Ethical Disclosures

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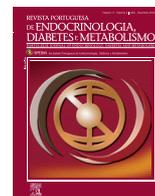
Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of patient data.

Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

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Artigo Original

Sistemas de Infusão Contínua de Insulina Subcutânea: Experiência de um Centro Terciário



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Sistemas de Infusão de Insulina

R E S U M O

Introdução: Os sistemas de infusão contínua de insulina subcutânea (SICIS) constituem uma opção no tratamento da diabetes mellitus tipo 1 (DM1), exigindo grande grau de motivação por parte do doente e acompanhamento permanente por uma equipa multidisciplinar. O objetivo foi avaliar o controlo metabólico e complicações agudas dos doentes com SICIS seguidos numa consulta de especialidade do HSM, colocados até 31 de Dezembro de 2013.

Métodos: Estudo retrospectivo, não comparativo. Extração de dados a partir dos processos clínicos. Tratamento estatístico em Excel 2010 e SPSS 21.

Resultados: Incluíram-se 46 doentes, 33 (77,1%) do sexo feminino, média de idade $38,5 \pm 9,9$ anos, média de idade de diagnóstico de DM1 $16,5 \pm 8,5$ anos e média de idade de colocação de SICIS $35,5 \pm 9,5$ anos. O motivo de colocação do SICIS foi: preconceção/gravidez em 14 (30,4%), mau controlo metabólico em 12 (26,1%) doentes, hipoglicémias graves em sete (15,2%), variabilidade glicémica em cinco (10,9%), baixas doses de insulina em quatro (8,7%) e flexibilidade de estilo de vida em quatro (8,7%). A média da HbA1c e do colesterol total prévia/posterior à colocação do SICIS foi, respetivamente $7,7\% (\pm 1,1\%) / 7,5\% (\pm 0,8\%)$, $p = 0,187$, e $185,3 \text{ mg/dL} (\pm 29,5 \text{ mg/dL}) / 177,0 \text{ mg/dL} (\pm 39,9 \text{ mg/dL})$, $p = 0,811$. A média do peso antes/depois do início do tratamento com SICIS foi $66,4 \pm 11,8 \text{ kg}$ e $65,9 \pm 10,4 \text{ kg}$, $p = 0,6$, respetivamente. A média de consultas médicas/ano por doente foi 3,6. Verificou-se um caso de hipoglicemia grave e um caso de complicações cutâneas locais (infecção cutânea). Não se verificou nenhum caso de cetoacidose diabética.

Conclusão: Embora não significativa, verificou-se uma descida da HbA1c e dos triglicéridos após colocação de SICIS, sem um aumento significativo do peso e sem ocorrência de complicações agudas.

Continuous Subcutaneous Insulin Infusion Systems: The Experience of a Tertiary Center

A B S T R A C T

Keywords:

Diabetes Mellitus, Type 1

Glycated Hemoglobin A

Infusions, Subcutaneous

Insulin

Insulin Infusion Systems

Introduction: Continuous subcutaneous insulin infusion systems (CSII) are an option in the treatment of type 1 diabetes (DM1). They require an high degree of motivation by the patient and a close follow-up by a multidisciplinary team. The objective was to evaluate the metabolic control and acute complications of patients under CSII in our Hospital.

Methods: Non-comparative, retrospective study. Data extraction from clinical processes. Statistical analysis in Excel 2010 and SPSS 21.

Results: 46 patients were included, 33 (77.1%) females and 13 males (22.9%), mean age 38.5 ± 9.9 years old, mean age at diagnosis of DM1 16.5 ± 8.5 years old and mean age when the CSII was started

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