The greater omentum as a site for pancreatic islet transplantation

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Abstract

The greater omentum is a highly vascularized anatomical structure in the peritoneal cavity. Its main components are connective, adipose and vascular cells, along with specialized immune cells. The omentum functions as a site for fat accumulation, it has adhesive properties to control traumatized and inflamed tissues, and a function in local hemostasis, immune responses, and revascularization. Other functions include the absorption of fluids, the phagocytosis of particulate matter, and foreign body reaction. The omentum is catalyzing significant interest for its potential as a site for pancreatic islet and cell transplantation. Our knowledge about this structure, its functions, and its potential as a site for transplantation is poised to grow in the coming years.

Anatomy and Histology of the Greater Omentum

The *greater omentum* (or *epiplón mayor*) is an anatomical structure resembling an apron, hanging in the peritoneal cavity, and usually extending over a large area of the abdomen[1] (Figure 1, 2). It arises from the greater curvature of the stomach, it crosses the transverse colon and descends in front of abdominal viscera, covering the intestines. There are two portions: the *gastrocolic ligament,* from the stomach to the transverse colon, and an area below the colon called *apron* (Figure 2). The omentum is composed of a frame of trabecular connective tissue, intermingled with arteries, veins, lymphatics, fat tissue, and lymphoid aggregates called "*milky spots*". Two monolayers of mesothelium contain all the above cell types and structures, with the exception of *milky spots* – where the mesothelium is interrupted. The macroscopic presentation of the greater omentum depends on the age of the individual, nutrition, pathological conditions and state of stimulation (such as in foreign body reactions, peritoneal dialysis). The *right* and *left Gastroepiploic arteries* provide blood supply to the greater omentum. Both arteries derive from the *celiac trunk* and pass the *greater gastric curvature.* They progressively branch out towards the stomach and the omentum, giving terminal vessels for the omentum through the right and left epiploic arteries. The omental margin blood supply is provided by numerous capillaries which may have minute anastomoses[2] (Figure 3). *Milky spots* present peculiar convoluted vascular structures termed *omental glomeruli*[3]. These microvascular structures show a characteristic architecture at the lateral branches of the *epiploic arteries* and their terminal branches. The vascular network is usually densely packed with various cells of the reticular system and fat cells. The outstanding feature is that the vascular walls have many fenestrations. Because of the discontinuous mesothelial lining on the milky spots, the glomerulus-like vascular structures are exposed to the peritoneal cavity[4]. The normal venous drainage parallels the arteries and empties into the portal system[5]. The gastroepiploic vein increases in diameter after receiving branches from stomach and omentum and empties into the superior mesenteric vein (83%) or in the first part of the splenic portal vein[6]. The terminal lymphatics form a web with irregular interconnections and with bulging saccular parts. This forms an unusual pattern shaped like flattened tubes[7]. Some of the

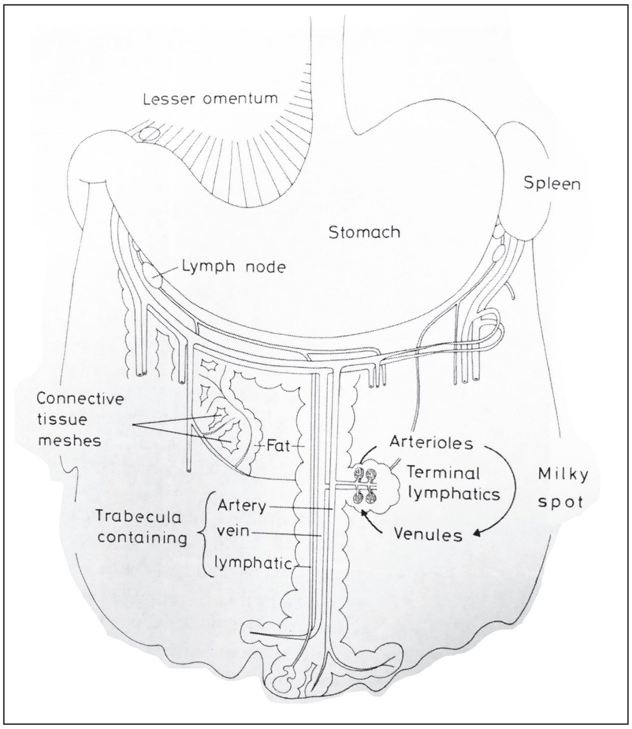

Figure 1. Scheme of the main constituents of the omentum (Reprinted from "The Greater Omentum", 1983, Edited by D. Liebermann-Meffert and H. White – with permission from Springer-Nature).

saccular terminals are located within the vascular system of *milky spots*, hence they also are exposed to the abdominal cavity because of the gaps in the mesothelial lining[8]. The main cellular components of the *greater omentum* are adipose and connective (mesenchymal) cells. The extracellular matrix is composed of collagen, elastic and reticular fibers, connected by microfibrils. Blood vessels, lymph vessels, and nerve fibers pass through this mesh. The omentum loose connective tissue is areolar, as it presents fixed cells (fibroblasts, fibrocytes, fat cells, pericytes) and mobile cells (histiocytes, monocytes, plasma cells, lymphocytes, eosinophilic granulocytes, mast cells). Fat cells are the most numerous cellular population, and their mass increases significantly in individuals with high Body Mass Index (Figure 4)[1].

Embryological development

The embryonic *mesoderm* is a cell layer that lines the body cavity *(coelom*) in amniotes. The *mesoderm* gives rise to multiple derivatives, including the *mesothelium* - a layer of cells that remains as a lining of the *abdominal cavity*, *pleura, mediastinum, and pericardium*. The *mesothelium* lining

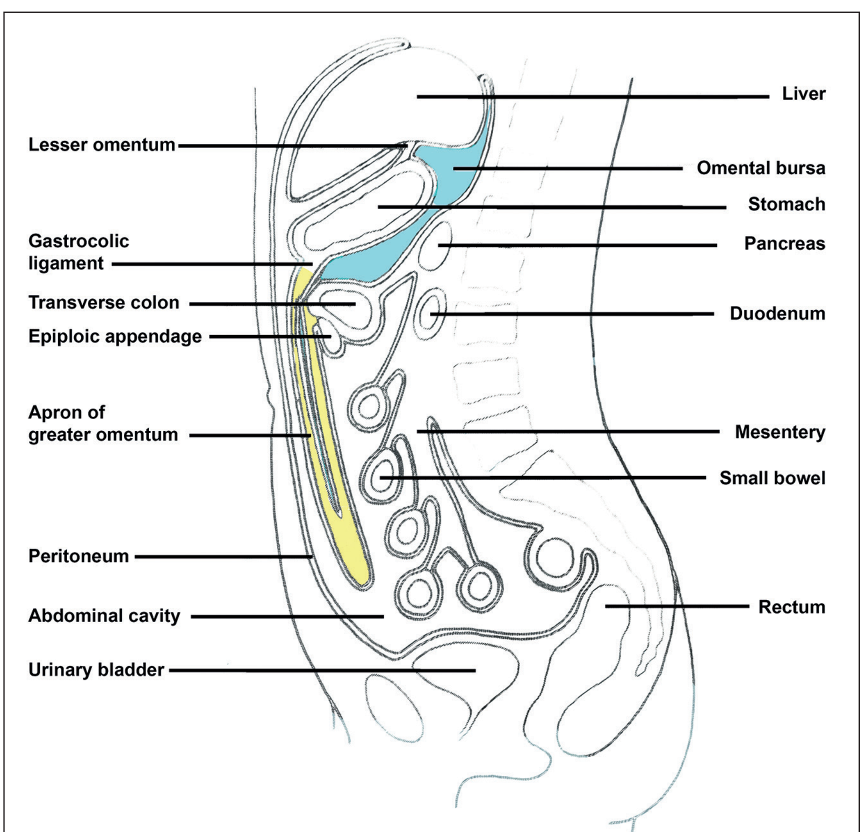

Figure 2. Diagram showing peritoneal reflections and topographical relations of the omentum in the sagittal section in humans (Edited from "The Greater Omentum", 1983, Edited by D. Liebermann-Meffert and H. White – with permission from Springer-Nature).

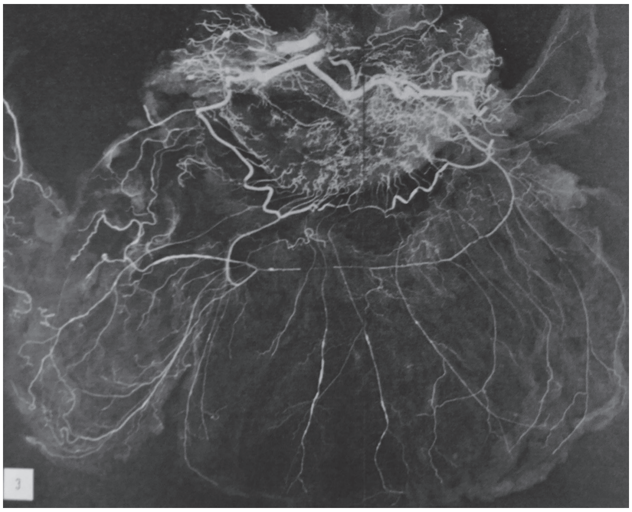

Figure 3. Vasculature of the Greater omentum in a human donor, imaged via angiography with barium gelatine. (Reprinted from "The Greater Omentum", 1983, Edited by D. Liebermann-Meffert and H. White – with permission from Springer-Nature).

the *abdominal cavity* is associated with a layer of connective tissue, and these tissues are collectively termed *peritoneum.* The *peritoneum* forms a serous membrane covering the organs in the *abdominal cavity.* A double fold of peritoneum constitutes the *mesentery*, that attaches the intestines to the wall of the abdomen (interestingly, the *mesentery* has been recently proposed for reclassification as an organ[9]). The portion of the *dorsal mesentery* that attaches to the greater curvature of the stomach is known as the *dorsal mesogastrium* (Figure 5). This structure subsequently expands, 'balloons' and then 'deflates', giving rise to an apron-like structure (a double layer of *peritoneum*) that is known as the *greater omentum*[1]. The rotation of the primitive stomach and the folding of the dorsal mesentery containing the spleen and pancreas form a dependent large inferior recess know as the *lesser sac*[10]. The g*reater omentum* is thus one of the omenta deriving from the folding of the *peritoneum;* it is located between the *greater sac* (*peritoneal cavity proper*) and the *lesser sac* (*omental bursa*) of the *abdominal cavity.* A fusion of the double layer of *peritoneum* most likely occurs, giving rise to the adult *greater omentum*[11] (Figure 2).

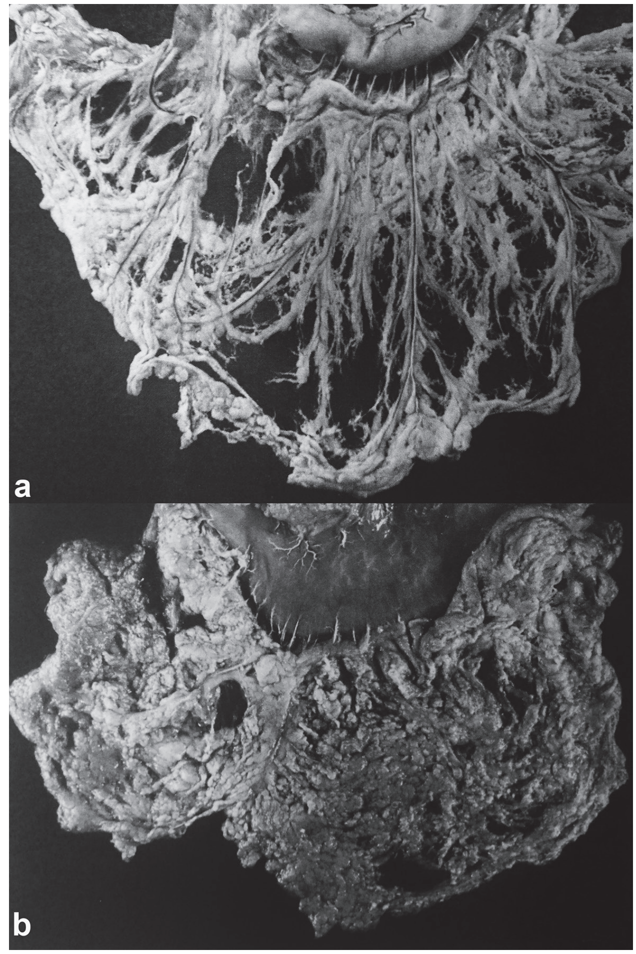

Figure 4. Adult human omentum from (a) a 36-year-old donor with a lean omentum and (b) from a 69-year-old donor with heavy deposition of fat in the omentum. (Reprinted from "The Greater Omentum", 1983, Edited by D. Liebermann-Meffert and H. White – with permission from Springer-Nature).

Physiology, Function, and Pathophysiology of the greater omentum

The physiological function of the omentum is still unclear but it is believed to be connected to the unique structure of its microcirculatory system. In pathological conditions, the omentum performs functions aimed at preserving body homeostasis[12,13]. The omentum absorbs particles and has an important role in combating abdominal infections (Morison called it the "abdominal policeman"[13]). During episodes of peritonitis, the omentum rapidly clears bacteria and foreign material that have penetrated into the peritoneal cavity[14]. Effector mechanisms are mediated by macrophages, neutrophils and, probably, B-lymphocytes. Macrophages are contained within the milky spots, and from there they can migrate into the peritoneal cavity via the openings in the mesothelial layer[15]. These macrophages phagocyte particles and bacteria from the peritoneal cavity. Subsequently, neutrophils can be recruited from the circulation, extravasate in the

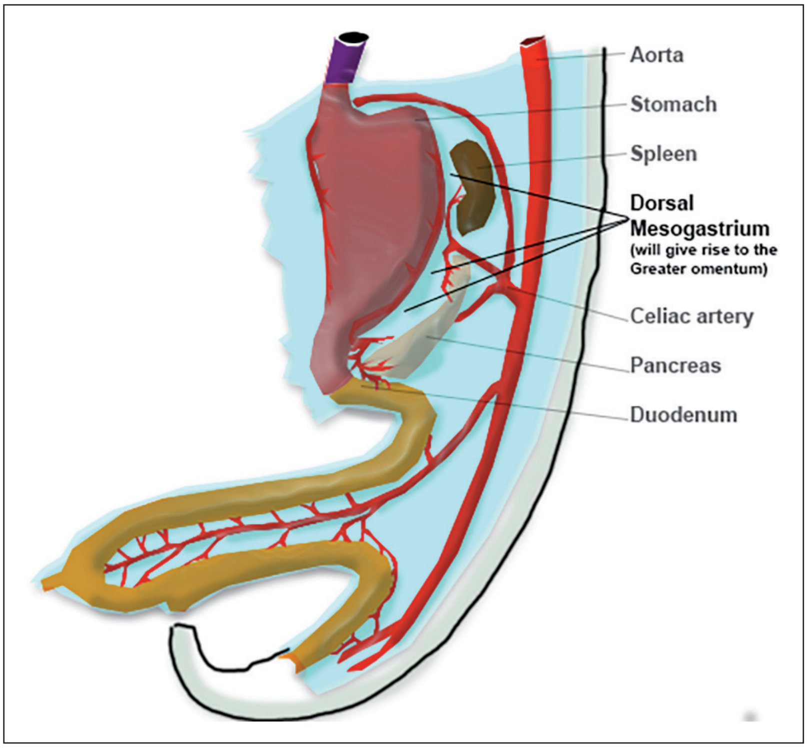

Figure 5. Schematic of the human embryo showing the disposition of developing organs and the location of the *dorsal mesogastrium*, that will give rise to the *greater omentum*.

milky spots and exudate in the peritoneal cavity to perform anti-microbial functions[16,17]. The omental functions of adhesiveness and cohesiveness are fundamental during mechanical trauma, tissue ischemia, intra-abdominal infections or reduced peristalsis[18]. Injury to the serosal membranes causes an immediate exudation of albumin, globulin, and fibrinogen that, once activated, become fibrin. 3 hours after the exudative phase, the adhesion phase starts. This is characterized by ingrowth of fibroblasts and capillaries, and it occurs at a pace that is faster than adhesions observed between other abdominal viscera[19]. The omentum also has the ability to reduce hemorrhage from injuries and to absorb fluids from the peritoneal cavity. Detailed investigation in more recent years has shown that it is able to encapsulate infarcted organs [20]. Pirone and Wilkie observed that polymorphonuclear leukocytes and mesothelial cells from the omentum enter the infarcted organ and through the ingrowth of capillaries determine its transformation into scar tissue[21]. The study of the chemical composition of irrigation fluids indicates that exposure, microsurgical injury, and other forms of trauma in the omentum consistently determine an inflammatory and vasodilatory response; this can cause higher permeability, augmented fluid filtration and increased local capillary pressures[22]. Microvascular studies show that the exchange flows are extremely efficient, if not the most efficient among those observed in the human body[22]. Under steady-state conditions, most of the fluid passing the capillary barrier in the omentum seems to become lymph. Hence, the liquid originating from the omental microcirculation does not return directly to the blood but passes through the lymphatic system.

Pathology

The greater omentum can present congenital abnormalities, and is susceptible to inflammatory disease, infarction, primary tumor and tumor metastases. *Omentitis* in one of the most frequent diseases of the omentum. The term *omentitis* indicates an inflammatory process of the *greater omentum* (the term *epiploitis* is instead used to indicate an inflammatory process involving the *greater omentum*, the *lesser omentum* and the *appendices epiploicae)*[23]. Historically, *omentitis* has been classified in post-operative, post-traumatic or spontaneous forms[24]. The spontaneous form occurs with bacterial infection (e.g. Mycobacterium tuberculosis[25]), it can be due to visceral inflammation, compression, torsion, and infarction - or it can be idiopathic[26]. Inflammatory processes and fibrosis in the omentum can be due to fungi, actinomycetes[27] or parasites[28]. Actinomycetes infection can result from trauma or immunosuppression[29]. Parasites affecting the omentum include Trematodes, Cestodes, Nematodes (e.g. filarial nematodes), Pentastomids, and Protozoa (e.g. plasmodium species causing malaria[1], amoebae[30]). Another cause of inflammation that could attract the attention of the researchers is the reaction to the presence of foreign bodies[31]. This reaction is usually related to the presence of needles, drains, catheters, coproliths, or other particulate material; it is composed of macrophages and foreign body giant cells[31]. A similar foreign body reaction could occur after cell transplants with encapsulation technologies used to reduce immune reactions. Fibrosis and scar formation are frequently the final outcomes of the pathological states indicated above. The greater omentum is also subject to necrosis in case of acute pancreatitis[32]. Macroscopically the main lesions are characterized by fat necrosis – appearing as yellow-white and chalky foci that may be scattered all over the omentum. During this pancreatic inflammatory process, the peritoneal cavity accumulates a turbid fluid, which may become infected. The lesions are not pathognomonic because they may occur after duodenal perforation or traumatic injuries of adipose tissue. Normally, chronic pancreatitis does not determine omental lesions. Particular attention should be given to the omental torsion and infarction. Omental torsion is classified into primary (due to intrinsic causes)[33] and secondary (due to extrinsic causes). Despite being a rare condition, secondary torsion may occur much more frequently than primary. Torsion is frequently recorded as a secondary finding during abdominal surgery. Omental torsion can determine the throttling and strangulation of vessels. The sequelae resulting from this could be localized or generalized omentum necrosis. with hemorrhagic exudation and aseptic inflammation[33]. Scar tissue formation is usually observed if the foci of necrosis are small, whereas larger areas of necrosis lead to abscess formation[34]. Necrotic areas can form after appendectomy. The typical and gold standard treatment of omental infarction is the surgical resection of the necrotic areas associated with appendectomy[35]. As discussed in a separate paragraph, pancreatic islet transplantation in the omentum is currently performed by "rolling-up" (or "folding-up") the greater omentum. Omental infarction secondary to this surgical procedure has never been reported, but surgeons and investigators should be aware of the potential risk and should monitor recipients accordingly. Cells of the omentum can undergo benign or malignant transformation. When compared to other tumors, omental tumor has a relatively low prevalence. No systematic studies on omental benign tumors are available. Most of the omental benign neoplasms are small and observed intraoperatively[36]. The vast majority of malignant tumors localized at the omentum are metastases, frequently deriving from ovary, stomach and colon cancer. Less than 3% of the malignant tumors in the omentum are primary omental tumors[36]. Mihail-Gabriel Dimofte reported a rare case of Extra-gastrointestinal stromal tumors (EGISTs) in the omentum; the omentum is an unusual location for this tumor (1% of the EGISTs occur in the omentum)[37]. EGISTs have features similar to Gastrointestinal stromal tumors, they represent approximately 10% of all stromal cancers[38]. The insulin-like growth factor 1 receptor (IGF1R) and its ligands have an important pathophysiologic role in stromal tumors[39]. Islet transplantation in the omentum could determine inflammation and high local insulin concentration. Insulin at high concentration can activate IGF1R[40], triggering cell proliferation and antiapoptotic pathways. Inflammation and IGF1R activation could increase the risk of development of omental tumors. This risk should be taken into consideration.

Surgical Use

The rich vascularization and the vascular plasticity of the greater omentum have attracted the attention of many surgeons. The omentum has been used for protective and reconstructive surgery in conditions such as stomach and intestinal perfurations[1]. The omentum is currently being studied as a site for pancreatic islet transplantation.

Sites for Pancreatic Islet Transplantation

It is estimated that 4% of the world population is affected by diabetes mellitus and that 10% of diabetic patients have type 1 diabetes[41]. The prevalence of this disease is increasing. Insulin is the primary treatment method for diabetes. Insulin is a life-saving intervention, but it can determine hypoglycemic events. Approximately 5-10% of patients experience multiple, severe and unexpected episodes of hypoglycemia, which can have serious and life-threatening consequences. In such cases, pancreas transplantation is an alternative treatment option that is already in clinical use and remains the gold standard therapy for diabetes mellitus associated with end-stage kidney failure. A more recent alternative option is islet transplantation, which is less invasive than pancreas transplantation[42]. The manufacture of the islet cell product with an automated method[43, 44] and islet transplantation in T1D patients[45] are currently in Phase 3 clinal trials in the U.S.A[46]. Up to 80% of recipients of islet transplantation were reported to be insulin independent in the first year post-treatment. The long-term survival rate of transplanted islets remains low, although certain pharmacological treatments appear to be associated with significantly prolonged islet graft survival[47]. A set of obstacles will have to be overcome in order to enable a widespread use of islet transplantation, including: the low number of available and suitable donor pancreases, the substantial cost of the islet isolation procedure, technical difficulties in recovering large numbers of islets, limited engraftment, limited duration of insulin independence, allograft rejection, and autoimmunity. For these reasons, as of today only a limited number of islet transplantations can be carried out[48]. It will be essential to identify a high-yield source of beta cells, durable over the time and that can be transplanted with little or no immunosuppression[49]. Moreover, the transplantation strategy will have to be improved with the aim of maximizing engraftment and function. The implantation site of choice impacts islet engraftment and function[50]. Ideally, the transplant site should reduce or avoid the instant blood-mediated inflammatory reaction (IBMIR), it should be well-vascularized, favor islet revascularization, have an appropriate oxygen tension, a suitable pH, an appropriate clearance of toxic metabolites, and access to nutrients. Also, it should enable islet function and good glycemic control, possibly using a low number of cells. Ideally, it should also protect the graft from the cellular immune response[51]. Desirably the transplant site should be easily accessible, to enable minimally invasive procedure. Furthermore, the islets should not be dispersed, so that they could be easily studied and eventually removed.

Pancreatic Islet Transplantation in the Liver

Currently, the liver is the site of choice for pancreatic islets transplantation. The technique of intraportal islet transplantation for engraftment into the liver was pioneered by Paul Lacy in 1973[50,52-54]. The first case of a diabetic patient receiving allogeneic islet transplantation in the liver and reaching insulin independence was reported in 1990[55]. This procedure is considered uninvasive, or minimally invasive. Bleeding, portal venous thrombosis, and gallbladder puncturing remain potential risks[56] but they are minimized by close adherence to the standard protocols for heparinization, obliteration of the catheter tract, and use of ultrasound guidance[57]. At 5 years post-transplantation, most of the patients that receive intraportal islets infusions maintain functioning islet grafts in the liver, but only 10% of them remain insulin independent (data from the CITR - Clinical Islet Transplant Registry[58,59]). Insulin independence at 3 years after transplant improved from 27% in the early era (1999-2002) to 37% in the mid era (2003-2006) and to 44% in a more recent era of islet transplantation (2007-2010)[59]. Besides this, the function of transplanted islets has the highly beneficial effect of abating the risk of severe hypoglycemic events – even when islet function is limited[46]. Nevertheless, the efficiency in yielding and maintaining insulin independence is certainly suboptimal. This limited efficiency is partly due to the loss of islet mass early after infusion. The causes of this important loss, approximately 60% of cells immediately after injection[60], are connected to the intraportal transplant method and to the target site – the liver[61]. IBMIR, thrombosis into the liver sinusoid, and hepatic tissue ischemia are frequently observed[61]. Transient mild increases of alanine transaminase and aspartate transaminase levels have been reported in about 50% patients undergoing intraportal islet transplant: these are probably associated with liver thrombosis and ischemia, and usually normalize in 1 month[62]. More than 20% of recipients show hepatic microsteatosis on ultrasonography, MRI and liver biopsy[63]. The islets transplanted into the liver are definitely exposed to higher concentrations of immunosuppressive drugs. Many of these agents can inhibit angiogenesis and are toxic for β-Cells, impairing their engraftment and function[64,65]. The awareness of these limitations has stimulated the search for alternative sites for pancreatic islet transplantation.

Alternative Sites for Pancreatic Islet Transplantation

Several sites alternative to the liver have been investigated. Some of them enable extravascular transplantation, others could be immune privileged. Alternative sites considered for islet transplantation include: thymus[66], bone marrow[67], testis[68], the anterior chamber of the eye[69], pancreas[70], gastric submucosa[71], muscle[72], subcutaneous space[72], spleen[73], kidney capsule[74,75], and omentum[76-78]. Despite the success of experiments in animals, only a few alternative sites have been tested into the clinical setting: the muscle of the forearm[79], the bone marrow[67], and the omentum[78].

The pancreas should offer the most appropriate environment for islet transplantation. Injection into the pancreatic parenchyma showed that, when compared to liver transplantation, a lower number of islets was sufficient to revert diabetes[80]. Islets transplanted in the pancreas receive a better oxygenation and were found to be metabolically superior to those transplanted into the liver[81]. The problems of transplantation into this site remain the invasiveness of the procedure, the risk of pancreatitis, and the recurrence of autoimmunity. The first could be overcome by minimally invasive endoscopic approaches. Pancreatitis can be extremely dangerous. Moreover, autoimmunity may recur more rapidly at this site. Islet transplantation into the gastrointestinal wall was found to be superior when compared to intra-liver transplantation in hamsters[71]. Bone marrow, pancreas and gastrointestinal wall certainly merit further investigation. Pancreatic islets transplanted in the spleen would be exposed to an environment similar to that of the pancreas. Despite good oxygenation and insulin drainage in the portal system, islets transplanted into the spleen did not show particular advantages over the liver in primates[82]. The kidney subcapsular site can be considered the gold-standard site for islet transplantation in rodents[83]. This site has a relatively poor oxygenation and nutrition supply. Other intra-vascular infusion experiments have been performed, including transplantation into the lung (systemic venous circulation), and infusion into the celiac artery. Although the arterial infusion should offer increased oxygenation and nutrition to the transplanted islets, islet survival was found to be superior after infusion in the portal system[84]. Islet grafts in the lung showed a good graft survival in animals[85] but the risk of thrombosis and IBMIR remain considerably high. Experiments in rats showed a long-term β-cell survival using the femoral bone marrow as a transplant site, with C-peptide control for more than 30 days[86]. The intramuscular site is easy to access and easy to monitor, and it has already been tested for parathyroid autotransplantation. A prevascularized site engineered in the intermuscular space enabled the efficient engraftment and function of islets in rats[87]. In 1997, Stegall reported the findings in three T1D patients that received pancreatic islet allografts in the forearm, under the muscle fascia. The islet dose was subtherapeutic, and the biopsies of the grafts were explanted at 7 and 14 days after transplantation. Two of the three grafts showed a mononuclear cell infiltrate suggestive of recurrence of autoimmunity[79]. To reduce immunogenicity and recurrence of autoimmunity against islet grafts, transplantation into an immune-privileged site would be desirable. The site should also have a sufficient volume to enable transplantation of a clinically relevant number of islets without substantial damage to normal function. Interesting studies found that co-transplant of islets with Sertoli cells delayed rejection in the absence of immunoppression[88, 89].

Pancreatic Islet Transplantation in the Omentum

Ferguson and Scothorne proposed the strategy of islet transplantation in the greater omentum in 1977[76]. Free floating islets were directly positioned onto the surface of the omentum, and the omentum was subsequently folded[76]. The investigators observed that islets transplanted in the omentum survived longer than islets transplanted in the liver[76]. The first studies in patients were performed by the group of Drs. Altman, Bethoux, Cugnenc, and Chretien in 1988-1989[90, 91]. Three T1D patients received allogeneic islet transplantation via embolization in a branch of the right gastroepiploic artery irrorating the omentum. *De novo* insulin production was observed in all cases. In one of these patients, islet transplantation was combined with liver transplantation. This case was a remarkable success: with insulin independence gained at 7 months and maintained at 15 months post-transplant, this was one of the first cases of long-term insulin withdrawal after an islet graft[91]. After these pioneering studies, other surgical approaches have been developed for islet implantation in the omental site. One strategy utilized a sequential approach: 1) a cell pouch device was wrapped in the omentum, 2) the device received vascularization, 3) pancreatic islets were implanted in the preimplanted cell pouch[92]. Another strategy termed omental roll-up was developed. This technique consists in the preparation of a coagulum of autologous plasma with islets and vascular endothelial growth factor (VEGF), and in the positioning of this coagulum onto the omentum. The omentum and the islets-containing coagulum are subsequently rolled up to present the islet layer with two omental surfaces for engraftment and to prevent the spreading of islet cells into the abdominal cavity[93]. Another strategy was developed and tested in non-human primates: islets were seeded on a synthetic scaffold and transplanted in an omental pouch. Islet engrafted in the omentum and survived for long periods of time[94]. Islet engrafted in the omentum were found to release insulin (c-peptide) at levels comparable to those of islets transplanted in the liver[94]. The team of the Diabetes Research Institute at the University of Miami started testing a strategy based on creating a resorbable scaffold comprising autologous plasma, islets, and thrombin[77]. An evolution of these initial preclinical findings was recently tested in the clinical setting and the first clinical case of islet transplantation onto the omentum was reported, as part of an ongoing clinical trial (ClinicalTrials.gov ID: NCT02213003)[78]. In August 2015[95], a 43 years old T1D patient underwent transplantation of allogenic islet in a degradable biologic scaffold onto the greater omentum[78]. Allogeneic islets were combined with autologous plasma and laparoscopically layered onto the omentum. The omentum was subsequently folded over to avoid distribution of the islets in the abdominal cavity. Recombinant thrombin and another layer of autologous plasma were layered over the islets. The induction immunosuppression regimen consisted of anti-thymocyte globulin and etanercept, and the maintenance immunosuppression regimen consisted of mycophenolate sodium and tacrolimus. Tacrolimus was switched to sirolimus 8 months after transplantation due to a side effect. The patient was followed up for 1 year. The patient showed a rapid gain of glycemic control, became insulin-independent at day 17 post transplantation, and remained insulin-free at 12 months post transplantation. Glycemic control remained stable at 6 months post-transplant, and showed a minor deterioration at 12 month post-transplant. No episodes of hypoglycemia were observed in the post-transplant period[78]. Multiple clinical trials are currently testing safety and efficacy of islet transplantation into the omentum (NCT02213003, NCT0282106, NCT02803905, and NCT00798785) (see ClinicalTrials.gov[96]).

Advantages and Limitations of Islet Transplantation in the Omentum

Preliminary observations suggest that islet transplantation in the omentum could be simpler than islet transplantation in other sites. Clinical trials will provide information about the safety and efficacy of this strategy. Animal experiments have shown that islet grafts survive longer in the omentum, compared to islets grafts in the liver[76]. Rapid correction of diabetes and good glycemic control have been observed[78]. Compared with the intraportal infusion technique, this procedure is expected to circumvent the IBMIR reaction[76]. The omentum has a high vascular density and good arterial supply, but further studies will be required in order to understand how long transplanted islets will remain in hypoxic conditions, and how rapidly islets will be revascularized. The level of oxygenation of islets transplanted in the omentum is still debated. Some authors have proposed that the revascularization in the omentum is delayed and that this could interfere with the metabolic outcome[97]; the initial islets loss is mainly due to the hypoxia secondary to the delayed revascularization, and it is independent of an inflammatory or immune-mediate reaction. Espes and colleagues reported contrasting findings: the initial hypoxia could stimulate the engraftment, the angiogenesis and the innervation of the islets yielding a superior functionality when the newly formed vessels are fully functional[98]. Additional studies will be required to clarify the aspects of hypoxia and oxygenation in islet grafts in the omentum. Unknown is also the potential effect of recipient BMI and amount of adipose tissue present in the omentum on islet engraftment and function (see Figure 4). The abundance of adipose tissue could impact negatively the oxygenation and revascularization of the graft, potentially causing partial graft loss or functional alterations. A potential advantage of the omental site could be that islets would be exposed to lower levels of diabetogenic immunosuppressive drugs, since orally administered immunosuppression produces relatively higher concentrations of potentially beta cell toxic drugs in the liver[99]. Additional studies will be required to test variables involved in islet engraftment and long-term function in the omentum, to optimize the strategy in this alternative transplant site. As we indicated in previous paragraphs, the omentum has a natural disposition to respond to foreign bodies with a strong inflammatory reaction. Such reactions may occur if certain scaffolding or encapsulating materials are combined with pancreatic islets. Islet hormones released into the venous system of the omentum would have an action similar to the physiological one, due to venous drainage in the portal system. Regeneration of β-cells innervation could also occur. Espes et al[98] observed a higher density of innervation and lower regeneration time in nude rats receiving human islets transplants. This innervation could make the release of insulin more similar to the physiologic one. In addition to this, unpublished preliminary reports suggest that β-cells maintain their differentiated state more efficiently when transplanted into the omentum, compared to the liver. This could contribute to the long-term function of β-cells. Patients with liver disease could definitely benefit from this type of transplantation. The procedure that is currently tested in clinical trials is minimally invasive. The surgeon has an easy access to the anatomical region of interest, laparoscopically drips the islets and the scaffold, and folds over an omental flap[78]. This maneuver is done to create a pouch that can protect the graft and avoid dissemination of islets in the peritoneal cavity. Islets could be easily removed for analysis. Unfortunately, the current imaging techniques do not enable non-invasive imaging of the transplanted islet tissue. Beta cell function (insulin, c-peptide), glycemia and related parameters (glycated HbA1c, required exogenous insulin dose, frequency of hypoglycemic events) indirectly indicate that islets transplanted in the omentum can control human T1D[78].

Conclusions

The omentum represents one of the most interesting sites for islet transplantation, an alternative to the liver. Additional studies will be required to clarify whether islet transplantation in the omentum is superior to transplantation into the liver. Factors such as details of the surgical strategy and characteristics of the recipient need to be considered with great attention. While the surgical strategy can be refined, the following variables and characteristics of the recipient require further investigation: the effect of the amount of fat tissue in omentum on engraftment and function of islet tissue, the effect of quality of the islet cell product, oxygen levels, previous abdominal surgery, presence of fibrosis or adhesions. The survival and function of transplanted islets will have to be analyzed in long-term studies, in order to characterize in depth this alternative transplantation site. When compared to the liver, this alternative site for islet transplantation has advantages and disadvantages. Ongoing and future studies will clarify whether or not the advantages outweigh the disadvantages.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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