Chapter 18

Biomaterials for Tissue Engineering Applications in Diabetes Mellitus

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.69719

Abstract

The search for ideal implants or alternative scaffolds is a challenge for biomedical science researchers, especially in diabetic patients. Many alternative bioactive materials have been used in the regenerative medicine, especially in patient with complex metabolic disorder as diabetes mellitus. Among them, we discussed the following alternative material scaffolds, including amniotic membrane (AM), homogenous demineralized dentin matrix (HDDM), platelet-rich plasma (PRP), and alloplastic materials as porous polyethylene and polyurethane. These biomaterials were applied in the craniomaxillofacial complex and liver injury, resulting in tissue regeneration and microstructural reconstruction due to their effective inductive and conductive properties. Additionally, diabetes disease and its general biophysical mechanism and systemic complications were described in order to improve the comprehension of the physiopathology of this comorbidity and its effects in the tissues. The AM, HDDM, and PRP in implantation sites initiated an inductive cascade as chemotaxis of progenitor cells, mitogenesis, angiogenesis, and differentiation into wide variety of cells. The cell recruitment, division rate, and differentiation of cell lines are under the direct control of several growth factors and stem cells which are present in these biomaterials. Further, some alloplastic materials have triggered satisfactory tissue responses when used in treatments of craniofacial deformities or in anatomical reconstructions.

Keywords: regenerative medicine, amniotic membrane, homogenous dentin demineralized matrix, platelet-rich plasma, alloplastic material, diabetes mellitus

1. Introduction

Diabetes mellitus (DM), a complex metabolic disorder, is a syndrome characterized by abnormalities in carbohydrate, lipid, and protein metabolism, which results either from a partial or an absolute insulin deficiency or from target tissue resistance to its cellular metabolic effects. This disease is characterized by the presence of few or by the absence of functional pancreatic β-cells in the islets of Langerhans and by a substantial reduction or inexistence of insulin secretion. This cellular dysfunction is an important defect in the pathogenesis of type 2 diabetes [1, 29].

Many strategies have been used as a biological dressing, an alternative bioactive material scaffold, and alloplastic material, including amniotic membrane (AM), demineralized dentin matrix (DDM), platelet-rich plasma (PRP), and alloplastic materials as porous polyethylene (porous PTFE) implant, in the degenerative complications in the diabetes disease. The AM is a high-throughput source for multipotent mesenchymal stem cells (MSCs) with the ability to differentiate into wide variety of cells, such as chondroblasts, osteoblasts, adipocytes and fibroblasts, myocytes, endothelial cells, neuronal cells, and hepatocytes, leading to formation of cartilage, bone, connective, muscle, blood vessel, nerve, and liver tissues, respectively. This membrane acts as a barrier prevents the entry of pathogens and toxins, preserves tissue structure, and consequently reduces the levels of local pro-inflammatory cytokines. The DDM is a bioactive tissue able to stimulate the bone repair process, to increase bone mass, and to improve bone microstructure without causing any rejection or infection. It is noteworthy that it acts as a reservoir for various proteins that are embedded within the matrix and are available to local cells, including bone morphogenetic proteins (BMPs), insulin-like growth factors I and II (IGF I and IGF II), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), transforming growth factor beta (TGF-β), and vascular endothelial growth factor (VEGF).

Based on the literature, we consider that the rich AM and DDM biological properties could be associated with other traditional graft materials, improving their biodynamic effects when implanted in host sites. Some alloplastic materials are well tolerated by the host tissues and present good stability in the implementation site, including porous polyethylene and polyurethane. These materials have been used in orthopedic, articular, orbital, cranial, and maxillofacial reconstruction. The presence of porous allows the ingrowth of the host tissue, which promotes better anchorage of the polymers in the host tissue.

Therefore, these alternative therapies may provide beneficial effects on tissue regeneration and reconstruction, in particular, in diabetes, since one of the main complications is delayed and abnormal repair process by accumulation of advanced glycation endproducts (AGEs) on tissues. These products cause severe widespread damage to tissue through upregulation of inflammation and cross linking of collagen and other proteins.

2. Diabetes mellitus

Diabetes mellitus is known as a metabolic disorder, characterized by deficiency of insulin secretion or action, leading to chronic hyperglycemia and disturbances of carbohydrate, fat,

and protein metabolism, may develop in, called diabetes mellitus (DM). According to the International Diabetes Federation, 8.8% of the adult population worldwide has diabetes. Of all individuals with diabetes, only 10–15% have type 1 diabetes mellitus (T1DM); type 2 diabetes mellitus (T2DM) is the most common form. However, T1DM is the most common form of diabetes in children (<15 years of age), and >500,000 children are currently living with this condition globally. The classification of diabetes mellitus disease defines both process and stage of the disease. The processes include type 1, autoimmune and nonautoimmune, with beta-cell destruction; type 2 with varying degrees of insulin resistance and insulin hyposecretion; gestational diabetes mellitus; and other types where the cause is known [1].

3. Development of the diabetes disease

Alterations in the molecular mechanisms of via insulin signaling may provide a deficiency, resistance, and/or decrease of insulin release into bloodstream, leading to development of the diabetes mellitus. To improve the comprehension of the physiopathology of this comorbidity and its effects in the tissues, firstly, it is important to know the biophysical mechanism involved in the glucose transport and the mechanism of insulin release, as well as the relationship of the glycation and diabetic complications.

3.1. Biophysical mechanism involved in the glucose transport

Fasting blood glucose levels are between 70 and 99 mg/dL in healthy individuals. These values can vary depending on food intake, renal function, physical activity, and the method used for testing. The major dietary polysaccharides, also called carbohydrates, for many species are starch and glycogen which are a storage form of glucose arisen from plants and animals, respectively. After food intake, the digestion process of vegetable (starch) and animal (glycogen) polysaccharides initiates from mouth, which are broken down by the salivary amylase (ptyalin), leading to the formation of oligosaccharides. Afterward, pancreatic and digestive enzymes break down these macromolecules to monosaccharides (glucose, fructose, and galactose) from upper small intestine. Posteriorly, these monosaccharides enter into enterocytes by luminal membrane transporters. It is worth highlighting that the pancreatic amylase is produced by the pancreatic acinar tissue, while the maltase, isomaltase, saccharase, and lactase are generated by the enterocytes. Pancreas is known as a glandular organ in the upper abdomen, which serves as two glands in one: a digestive exocrine gland (e.g., production of pancreatic amylase) and a hormone-producing endocrine gland especially composed of islets Langerhans. These islets are constituted of four hormone-producing cell types: insulin-secreting beta cells, glucagon-secreting alpha cells, somatostatin-secreting delta cells, and pancreatic, polypeptide-secreting F cells. Both the glands are vital to the body's survival (**Figure 1**).

Several factors can influence in the insulin secretion, including amino acids, fatty acids, hormones, and drugs; however, the blood glucose concentration levels are considered the main physiological regulators of insulin release. The glucose molecule ($C_6H_{12}O_6$) depends on a transporter protein to enter the cells, seeing that is impermeable to cell membrane. Thus, the glucose uptake from intestinal lumen occurs through ion-coupled membrane cotransporters

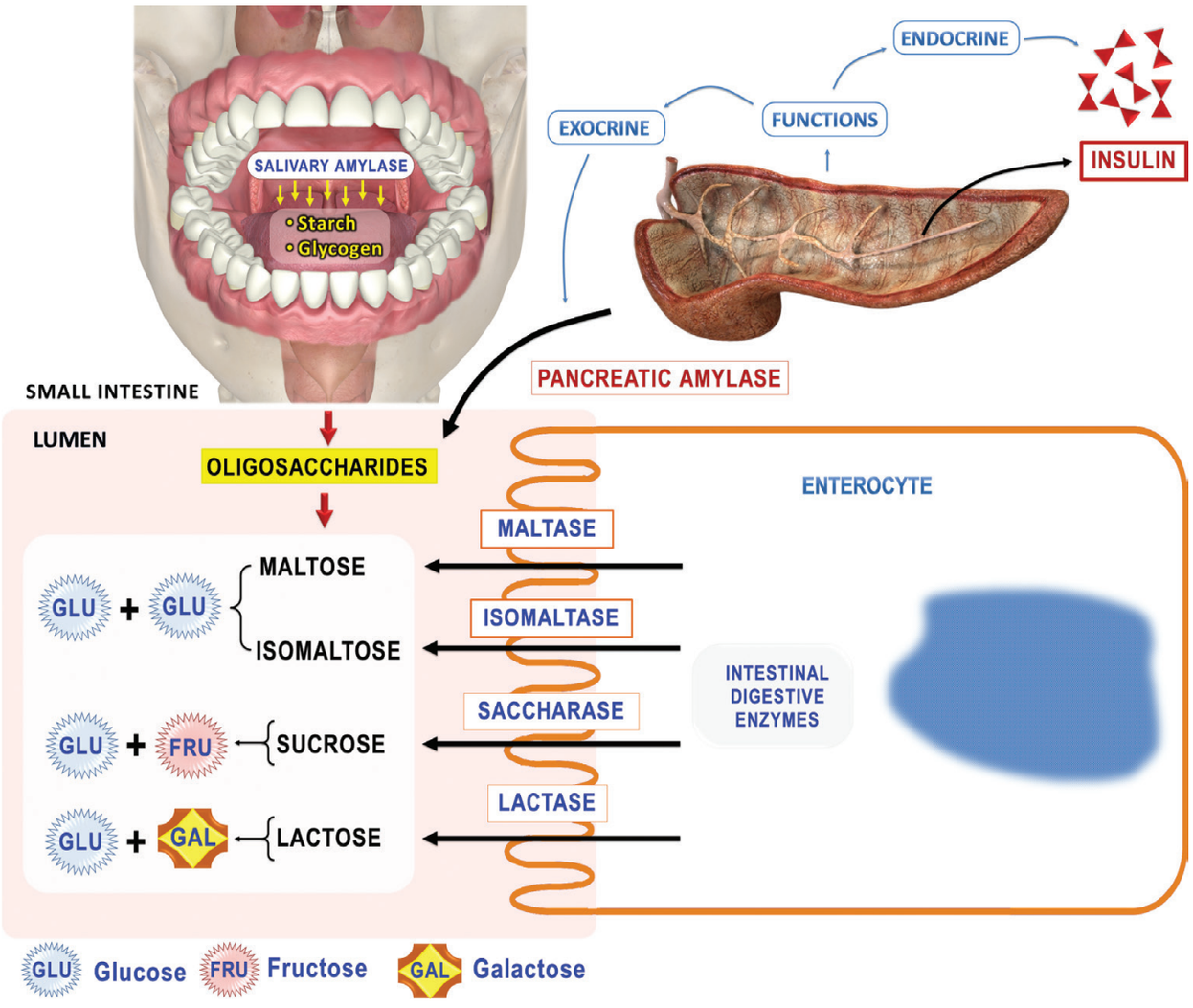

Figure 1. Diagram showing carbohydrate degradation by oral, pancreatic, and intestinal enzymes.

which are molecular machines that use the electrochemical energy of a transmembrane ionic gradient to energize the transport of another solute [37]. Among them, it is known as the type 1 sodium-glucose cotransporter (SGLT-1) that is located at the cell membrane of the apical region of the enterocytes. This cotransporter is coded by the SLC5A1 gene, which was the first mammalian cotransporter carrier protein to be identified, cloned, and sequenced [4].

The present review discusses the members of the sodium-glucose cotransporter (SGLT) gene family (the SLC5A gene family) have been identified in a broad range of tissues, including intestine, kidney, muscle, neurons, and thyroid [21, 36]. The SGLT-1 protein has two allosteric sites that carry a galactose or glucose molecule and sodium ions ($2Na^+$) into the cells, while fructose molecule passes across the luminal membrane through the GLUT-5 (fructose transporter). Both the transport proteins are found at the apical surface of the enterocytes in the small intestine [9]. The glucose transporters (GLUTs) are sodium-independent membrane transport proteins which carry particularly monosaccharides, including glucose fructose and galactose. Various members of solute-carrier (SLC) gene family have been found in

literature [28]. None of these transport mechanisms requires cell energy expenditure, characterizing a biological process of passive transport.

Considering the intestinal epithelial cells, the glucose entry depends on the electrochemical gradient of Na^+, as well as its translocation from luminal membrane to basolateral membrane. These differences of extracellular and intracellular concentrations of Na^+ are kept by the sodium-potassium pump. The potassium ions (K^+) into cells pass to extracellular matrix (ECM) through specific channels, located at the basal membrane that maintains pump activity. The sodium-potassium pump is an active transport mechanism which requires energy expenditure using adenosine triphosphate (ATP). The internal cell membrane potential of the enterocytes is negative in relation to the external cell membrane, typically about −70 millivolts. This voltage arises from differences in concentration of the sodium and potassium electrolyte ions, leading to glucose entry into cells. The glucose molecule passes into the extracellular matrix (ECM) through the glucose transporter-2 protein (GLUT-2). Then, it enters in the bloodstream due to the differences of gradient concentration between the ECM and blood capillary (**Figure 2**). Considering the biological property of the blood vessels, intercellular clefts, fenestrations, and cell membrane discontinuity of the endothelial cells also facilitate the gradient diffusion into bloodstream [24].

3.2. Mechanism of insulin release

As previous discussion, the elevated levels of blood glucose generate insulin release from pancreatic β-cells at the islets Langerhans, which plays a pivotal role in the glucose homeostasis and acts in a coordinated fashion on cellular events that regulate the metabolic and growth processes in the human body.

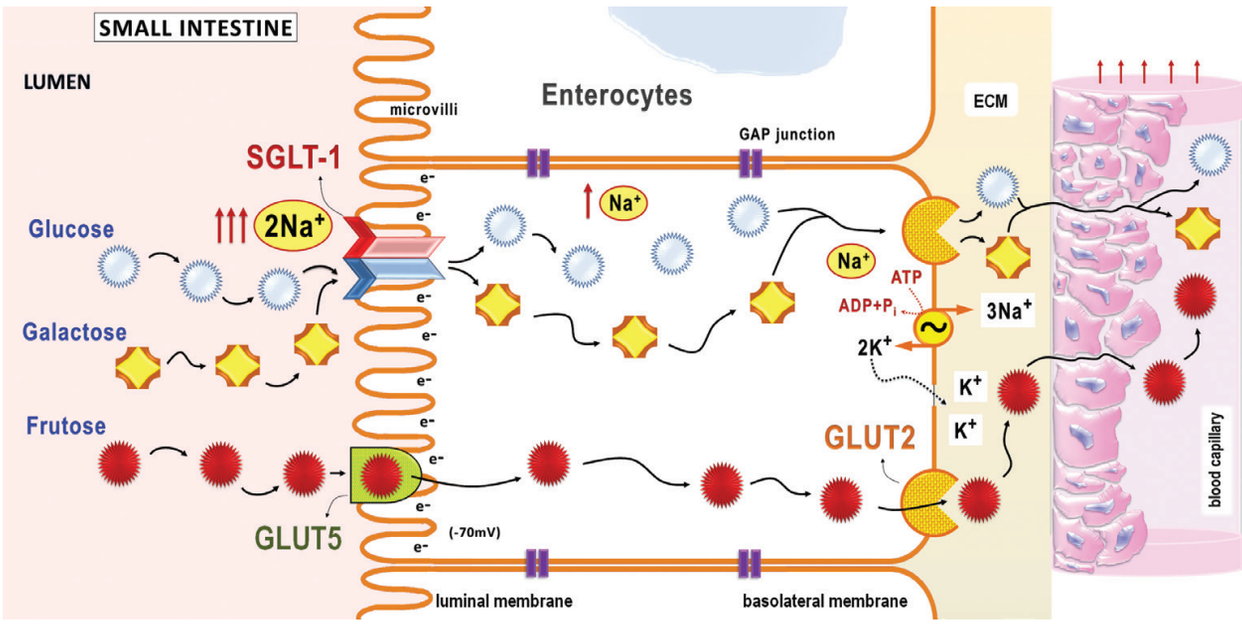

Figure 2. Diagram showing the glucose absorption by the enterocytes.

In humans, the threshold value for glucose-stimulated insulin secretion is about 100 mg/dL (5.6 mmol/L) of plasma glucose concentration. This hormone is secreted in a biphasic manner in response to a marked increase in blood glucose. An initial burst of insulin secretion may last 5 to 15 min, resulting from the secretion of preformed insulin secretory granules. This response is followed by more gradual and sustained insulin secretion that results largely from the synthesis of new insulin molecules.

The primary mechanism is through binding to sulfonylurea receptor (SUR-1) on functioning pancreatic β-cells. Afterward, binding closes the linked ATP-sensitive potassium channels (K_{ATP} channels), which leads to decreased potassium influx and subsequent depolarization of the β-cell membrane. This event provides voltage-dependent T-type calcium (Ca^{2+}) and sodium (Na^{+}) channel opening, resulting in an influx of Ca^{+} channel, as a consequence, causing translocation and exocytosis of insulin-secretory granules to the cell surface. Then, the insulin from the ECM enters into the bloodstream, following toward the target cells [5].

Another mechanism that promotes ATP-sensitive potassium channel closure is increased ATP levels, which are produced into two distinct metabolic pathways: glycolysis (anaerobic process) and mitochondrial respiratory chain (aerobic process). Initially, the glucose molecule passes across the β-cell membrane through the glucose transporter 2 (GLUT-2), and then, it is phosphorylated to form glucose-6-phospate (G-6-P) by two enzymes: hexokinase IV (HK-IV) or glucokinase (GK) of lower affinity for glucose and hexokinase I (HK-I) of higher affinity for glucose. However, the higher affinity enzyme is strongly inhibited by the G-6-P, transferring to the GK a key role in the glucose phosphorylation at the pancreatic β-cells. This process constitutes the first flux determining step for glycolysis. The G6P is broken down into 2-phosphoenolpyruvate by the pyruvate kinase which is transformed in two pyruvates molecules (glycolysis). After that, these molecules enter into mitochondria where two different biochemical processes occur, including the cycle of Krebs and the oxidative phosphorylation cycle. Finally, several ATP molecules are generated. The glycolysis and mitochondrial respiratory chain pathways result in the synthesis of 2 ATPs and 34–36 ATP molecules, respectively, totalizing about 36–38 ATP molecules/mol of glucose [5, 34]. It is noteworthy to highlight the promotor mechanisms to K_{ATP} channels closure lead to the insulin release into the blood stream (**Figure 3**).

After the insulin arrival onto target cells, it links to a specific cell membrane receptor, called insulin receptor substrate (IRS-1) protein, initiating a cascade of phosphorylation events. As a consequence, vesicles containing glucose transporter proteins, especially the GLUT-4, move to the cell surface. The high GLUT-4 level onto cell membrane leads to increase of glucose uptake. Depending on the cell activity, two processes can occur due to high concentration of intracellular glucose: glycolysis or glycogen synthesis. To elucidate better this mechanism, GLUT-4 is an insulin-stimulated glucose transporter that has the primary form of the transporter present in skeletal muscle tissue and adipose tissue. It is present in cells and in intracellular vesicles of the smooth ER. In target cells, the effect of insulin is to promote the translocation of GLUT-4 transporter from intracellular pool to cell membranes. As a result, more transporters are available in the plasma membrane, and glucose uptake by target cells is, thereby, increased.

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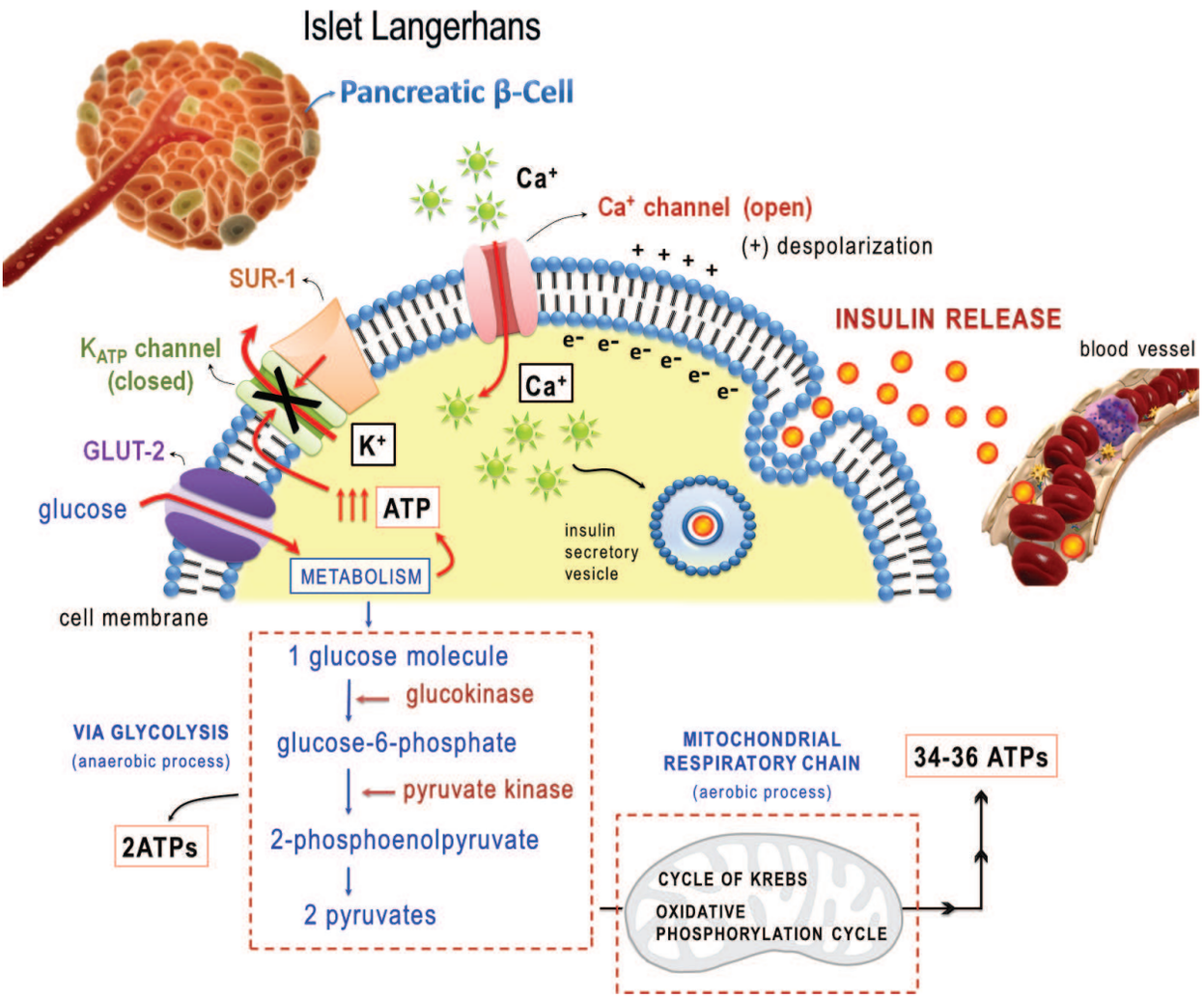

Figure 3. Mechanism of insulin release from pancreatic β-cell to bloodstream.

Based on these basic concepts, we can consider that methods for SGLT and GLUT inhibition can be considered an suitable alternative means of managing glucose control and, as a consequence, a further treatment option to control the diabetes disease.

3.3. Relationship of the glycation process and diabetic complications

Persistently elevated glucose levels during long-standing diabetes induce structural and functional changes in various proteins in the body, including plasma protein (albumin, globulins, and fibrinogen) and collagens, through a glycation or nonenzymatic glycosylation process [3, 23, 39, 44]. This process involves an excessive chemical attachment of sugar molecule (e.g., glucose or fructose) to proteins, lipids, and nucleic acids, without the involvement of enzymes. Various deleterious effects from glycation of plasma protein may be produced, including alteration in drug binding in the plasma, platelet activation, generation of oxygen free radicals, impaired fibrinolysis, and impairment in immune system regulation. On the other hand, the structural impairment in collagen alters the osteoblast differentiation, leading

to disorders of bone remodeling process and, as a consequence, skeletal fragility [20, 39]. The glycation and oxidation of lipids and nucleotides can also form a single product from various heterogeneous molecules (heterogeneous adducts) through amino-carbonyl reactions, known as advanced glycation endproducts (AGEs) [23, 27]. As the direct products of diabetic metabolic remodeling, AGEs are an important environmental medium for changes of cells, cytokines, and extracellular matrix components including collagens, proteoglycans, laminin, and vitronectin [11, 20]. These changes in the extracellular matrix cause specific alterations in bone formation and bone remodeling. Bone tissue turnover has been shown to be suppressed; studies have shown decreases in the percentage of osteoclasts and osteoblasts as well as a decrease in osteocalcin synthesis [8, 11, 16]. Moreover, AGEs exhibit the ability to inhibit cellular differentiation, proliferation, and migration, which could delay the repair process [20].

Therefore, the protein glycation, elevated level of AGEs accumulation in tissue collagen, and high plasma AGE concentration lead to major diabetic complications like retinopathy, nephropathy, neuropathy, atherosclerosis, degenerative and cardiovascular diseases, inflammatory arthritis, osteoporosis, susceptibility to infections, delayed tissue repair, and severe periodontal disease [3, 17, 39]. Other generic complications are impaired neovascularization and microvascular complications, resulting in ulcers and chronic nonhealing wounds with the characteristics of high amputation rate [20, 46].

Currently, the major concerns with the use of AGEs inhibitors as therapeutic agents are low effectiveness, poor pharmacokinetics, and undesirable side effects. Several AGEs inhibitors possess potent antiglycation activity and are devoid of undesirable side effects. These small molecules inhibitors can, therefore, serve as scaffolds for the development and designing of new AGEs inhibitors as clinical agents [23].

Studies have described that high levels of AGEs induce increased index values of oxidative stress in bone cells due to the absence of the counterbalancing effects of endogenous antioxidants [17]. Thus, it is considered that bone loss can occur as a result of activated osteoclastogenesis, attenuated osteoblastogenesis, and/or stimulated osteoblast apoptosis, which can be induced by the elevated intracellular levels of reactive oxygen species (ROSs) [13, 17]. ROSs produced either endogenously or exogenously are often associated with the principle of oxidative stress, which can attack lipids, proteins, and nucleic acids simultaneously in living cells [45]. This free radical or byproducts of an aerobic metabolism, including superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH), can confer reactivity to different biological targets. Increasing evidences have suggested that oxidative stress plays a major role in the pathogenesis of diabetes mellitus due to structural and/or functional damage of the pancreatic β cells [38, 45]. Some studies have described that the persistent hyperglycemia has reduced recruitment of mesenchymal stem cells (MSCs) toward the wounds, compromised their cellular differentiation, and affected the quantity of endothelial progenitor cells, preventing vasculogenesis and delaying the healing process [46]. Accumulating evidence also suggests that the impaired MSCs can compromise mobilization and function of bone cells, resulting in low bone turnover and formation [17].

Recently, alternative material scaffolds have been used to accelerate tissue repair process or to promote implant-based tissue reconstruction, besides the advent of stem cell therapy as a pivotal basis of tissue regeneration or replacing, bringing great hope to diabetic patients.

4. Biological and alloplastic materials for tissue engineering

The goal of tissue engineering is to create grafts that enhance tissue repair following trauma, infection, or neoplasm, and for developmental abnormalities; these procedures represent a challenge in surgery. To obtain effective and suitable tissue regeneration or osseointegration, the following are necessary: osteoprogenitor and osteoconductive cells, which offer potential to differentiate and facilitate the various stages of tissue regeneration, growth factors (GFs), and structural integrity with the absence of any kind of local infection [17].

As a compensatory factor, some biomaterials for tissue engineering with promotive properties, including amniotic membrane (AM), demineralized dentin matrix (DDM), platelet-rich plasma (PRP), and porous polyethylene (porous PTFE) in diabetic and nondiabetics experimental model were described as follows.

4.1. Diabetic experimental models

The main drugs widely used to induce diabetic experimental models are streptozotocin and alloxan. The cytotoxic action of both the diabetogenic agents is mediated by reactive oxygen species (ROS). The streptozotocin drug enters into pancreatic β-cells via a glucose transporter (GLUT-2) and causes alkylation of DNA. DNA damage induces activation of polyADP-ribosylation that leads to depletion of cellular NAD^+ and ATP. Enhanced ATP dephosphorylation supplies a substrate for xanthine oxidase, resulting in the formation of superoxide radicals as hydrogen peroxide and hydroxyl radicals. Furthermore, toxic amounts of nitric oxide are release, causing inhibition of mitochondrial aconitase activity and DNA damage and triggering the destruction and necrosis of these cells. The alloxan drug promotes the superoxide radical formation, which undergoes the dismutation to hydrogen peroxide. Thereafter, highly reactive hydroxyl radicals are formed by the Fenton reaction. The ROS action and the simultaneous massive increase of cytosolic calcium concentration cause a rapid destruction of the pancreatic β-cells [41].

Experimental models for monohydrate alloxan-induced diabetes in rabbits and rats were developed. The diabetes was diagnosed due to the blood glucose levels above 200 mg/dL (**Figure 4**). This drug, in particular, promotes destruction of the pancreatic β-cells and parenchyma disorganization with presence of atypical acinar cells, scarce secretion vesicles, atrophy, and a decreased number of Langerhans islets in some regions, leading to severe pancreas dysfunction and, as a consequence, the development of diabetes type 2. Three months after the diagnosis of diabetes in experimental models, general clinical complications can be found, including weight loss, polyuria, polyphagia, ketoacidosis due to accentuated hypoglycemia, convulsions, diabetic foot, acute dermatitis, erythematous, and ulcerated lesion associated with fungal and bacterial infections located in the submandibular region extending to trunk and neck regions, and intracranial abscess in regions of surgical defect due to impaired bone repair and susceptibility to infections. Severe chronic gingivitis can be also evidenced (**Figure 4**) [11, 13, 42].

It is important to consider that diabetic wounds exhibit impaired angiogenesis, reduced growth factor levels, and reduced chemotactic ability to recruit inflammatory cells to the

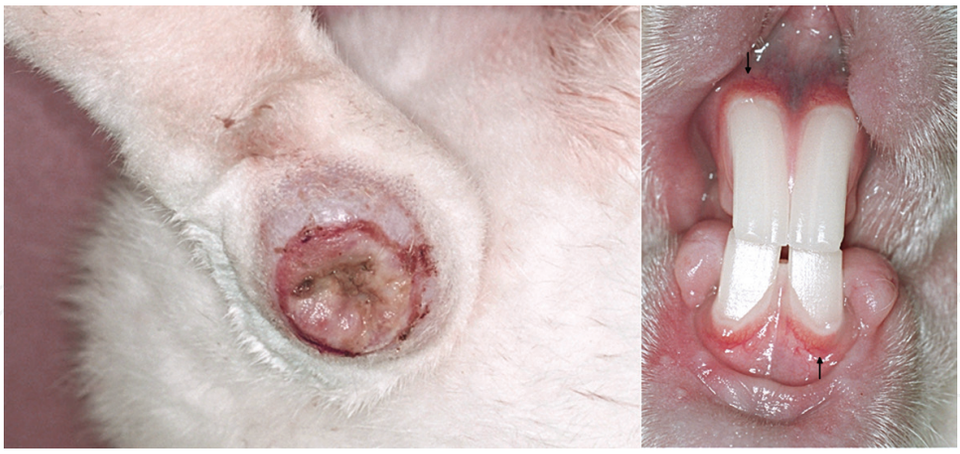

Figure 4. Classical clinical complications in diabetes showing diabetic foot and chronic gingivitis (arrows) in rabbit after 3 months persistent hyperglycemia.

wound, besides that the poor vascularization and maintenance of a chronic inflammatory state limit the healing capacity. Therefore, we discuss in this chapter some conductive and inductive materials for tissue engineering, including AM, DDM, PRP, and porous PTFE, which were applied in diabetic and nondiabetic experimental models or individuals.

4.2. Biological materials

4.2.1. Amniotic membrane (AM)

The AM is a tissue of fetal origin and is composed of three major layers: a single epithelial layer, a thick basement membrane, and an avascular mesenchyme that contain growth factors, cytokines, and other active substances [26]. AM has two types of cells of different embryological origins: amnion epithelial cells derived from embryonic ectoderm and amnion mesenchymal cells from embryonic mesoderm. It is adjacent to the trophoblast cells and lines the amniotic cavity. It can be easily separated from the underlying chorion, with which it never truly fuses at the cellular level. Its nutrition and oxygen are obtained from surrounding chorionic fluid, the amniotic fluid, and the fetal surface vessels. This structure protects the developing embryo against mechanical aggression, provides an environment where the embryo can grow without distortion by pressure from surrounding structures, and also plays an important role during parturition [15].

As a highlight of great potential for clinical application, the amniotic membrane has been widely used in regenerative medicine due to its effective biological properties (biocompatibility, low immunogenicity, anti-inflammatory, and antimicrobial activities), adequate physicomechanical action (permeability, stability, elasticity, flexibility, and resorbability), excellent tissue adhesion, easy delivery of biomodulatory agents including growth factors and genetic materials, and rich MSC source [22, 31, 33]. Current investigations described that pluripotent stem cell lines derived from AM have the ability to differentiate into endothelial and neuronal cells, osteogenic, chondrogenic, adipogenic, skeletal myogenic, hepatic lineages, and able suppress T-cell proliferation [19, 31, 35]. These properties show the greatest prospects

to clinical applications in regenerative medicine, which leads to processes of tissue replacing, engineering or regenerating, and preservation of organ functions [12, 26, 43].

Several researches developed in the Center of Biosciences Applied to Persons with Special Care Needs (CEBAPE) in the São Paulo State University (UNESP) has applied the AM as a biologic dressing and a bioactive scaffold material to treat oral mucositis, surgical hepatic resection areas in experiments *in vivo*, and wound areas from incisional and excisional biopsies of oral lesions originated of inflammatory and development processes. This membrane was also applied to stimulate the guided bone regeneration (GBR) in experimental bone defects and to accelerate the tissue repair.

The methods of preparation and storage of the human (h) and homogenous (H) AM were developed by the CEBAPE which are described in the literature [15, 18, 26, 43]. Additionally, the clinical procedures were performed in diabetic and nondiabetic patients or in different animal models, leading to highly favorable results that are reported as follows. We can prove its effects on the tissues through the clinical, biochemical, histological and immunohistochemical outcomes, in particular, in experimental models. As a xenogenic material, a human amniotic membrane (hAM) was used for guided bone regenerative on surgical defects in healthy rabbits. The biocompatibility and low immunogenicity of the hAM were shown since we evidenced newly formed bone tissue in intimate contact with hAM in several surgical defect areas and discrete infiltration of mononuclear inflammatory cells surrounding the hAM in some regions; moreover, its osteogenic and mitogenic effects were very evident (**Figure 5**).

Other application could be in oral biopsy areas to lesion diagnosis, especially in areas of difficult suture as alveolar bone ridge in maxilla and mandible. Studies also showed the use of hAM on wounds produced from incisional and excisional biopsies of alveolar gingiva of the upper premolar region and cheek mucosa, respectively. The diagnosis was plan lichen (inflammatory process) in the alveolar gingiva and intramucosal pigmented nevus (development process). The outcomes were highly satisfactory in both processes, inducing the rapid closure of

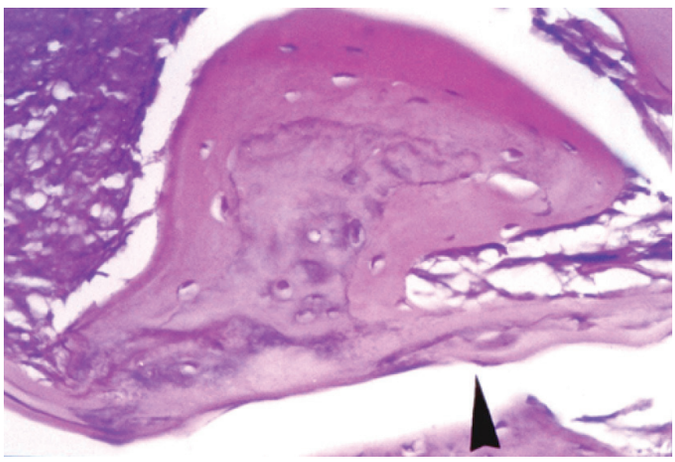

Figure 5. Human amniotic membrane (arrow-head) used as a bioactive xenogenic material which was applied in the guided bone regeneration on the surgical defect in rabbits: newly formed bone formation from the membrane and few infiltrations of mononuclear inflammatory cells, especially lymphocytes, were evidenced (Source: Gomes et al., [15]).

wounds due to stimulation of the tissue repair, relief of pain, and no sign of local infection [18]. Probably, relief of pain occurs due to its strong action of mechanism barrier and good stability on the wound surface, covering nerve endings.

In previous research using homogenous amniotic membrane (HAM) on the surface of surgical liver, resection in rats was performed. The HAM was obtained female rats by cesarean at the 20th day of pregnancy. Fetal amniotic membrane was separated aseptically from the chorionic membrane and rinsed several times in a sterile physiological saline solution and a phosphate buffer at pH 7.4 until the removal of all debris (**Figure 6**). After its laboratory preparation, the HAM was placed on the surface of surgical liver resection. Clinically, this membrane showed an immediate stability and a strong hemostatic action after its implantation on the wound. Histologically, the HAM behavior was observed in 10, 20, 30, and 40 days, showing the following results. Initially, the HAM was biocompatible to hepatic tissue once it intimately adhered to hepatic tissue in regenerative process; subsequently, it underwent metaplasia turning into a highly well-cellularized and vascularized tissue called aminohepatic tissue. Discrete infiltration of mononuclear inflammatory cells was seen surrounding this biological membrane. This histological characteristic was one of the prominent aspects that can suggest its low immunogenicity in surgically impaired liver tissue. HAM remnants can be found on the injured liver tissue surface in some specimens, after 40-day postsurgery (**Figure 7**). In biochemical analysis of plasma and tissue samples, the aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyltransferase (GGT) enzymatic levels were significantly low; in contrast, the alkaline phosphatase (ALP) enzymatic levels and the total protein concentrations were strongly high in the rats treated with HAM. Thus, angiogenic, mitogenic, and hepatic-protector effects of the HAM were proved, leading to a better microstructural reconstruction of the injured liver [12].

In our study, other beneficial application of the HAM was as a potent biological dressing in 5-fluorouracil-induced oral mucosites (OM) in rats (**Figure 8**). The pathophysiology of the analyzed OM and its histomorphological features were divided into four phases: inflammation (3 days), cell proliferation (7 days), tissue organization (14 days), and tissue repair (21 days). Among the periods of inflammation and cell proliferation phases, the HAM was incorporated with the wound surface, acting as a protective barrier against microbial infection and preventing any infection signs. Other aspects were discrete to moderate infiltration of inflammatory cells in the connective tissue and early total re-epithelialization in most specimens. The incorporated HAM into connective tissue was degraded and, then resorbed. Regarding the tissue organization and repair phases, the histological features were described the follow. At 14 days, discrete mononuclear inflammatory cells surrounding the connective tissue, muscle layer with normal aspect, a tissue maturation with regularly disposed, remodeled collagen fibers, and rare blood vessels were found. Finally, at 21 days, the oral mucosa showed normal aspects (**Figure 9**). Thus, we can consider that the HAM provides an excellent environment for cell proliferation and neovascularization, stimulating healing process and functioning as a promising biological dressing. Previous studies confirm the growth factors are found into amniotic membrane, including transforming growth factor-β1 and β2 (TGF-β1 and β2), basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), transforming growth factor-α (TGF-α), keratinocyte growth factor (KGF), and hepatocyte growth factor (HGF) [33], reinforcing our findings. Regarding the biodegradable property of the HAM, we hypothesize that the avascular stromal matrix of the HAM is similar

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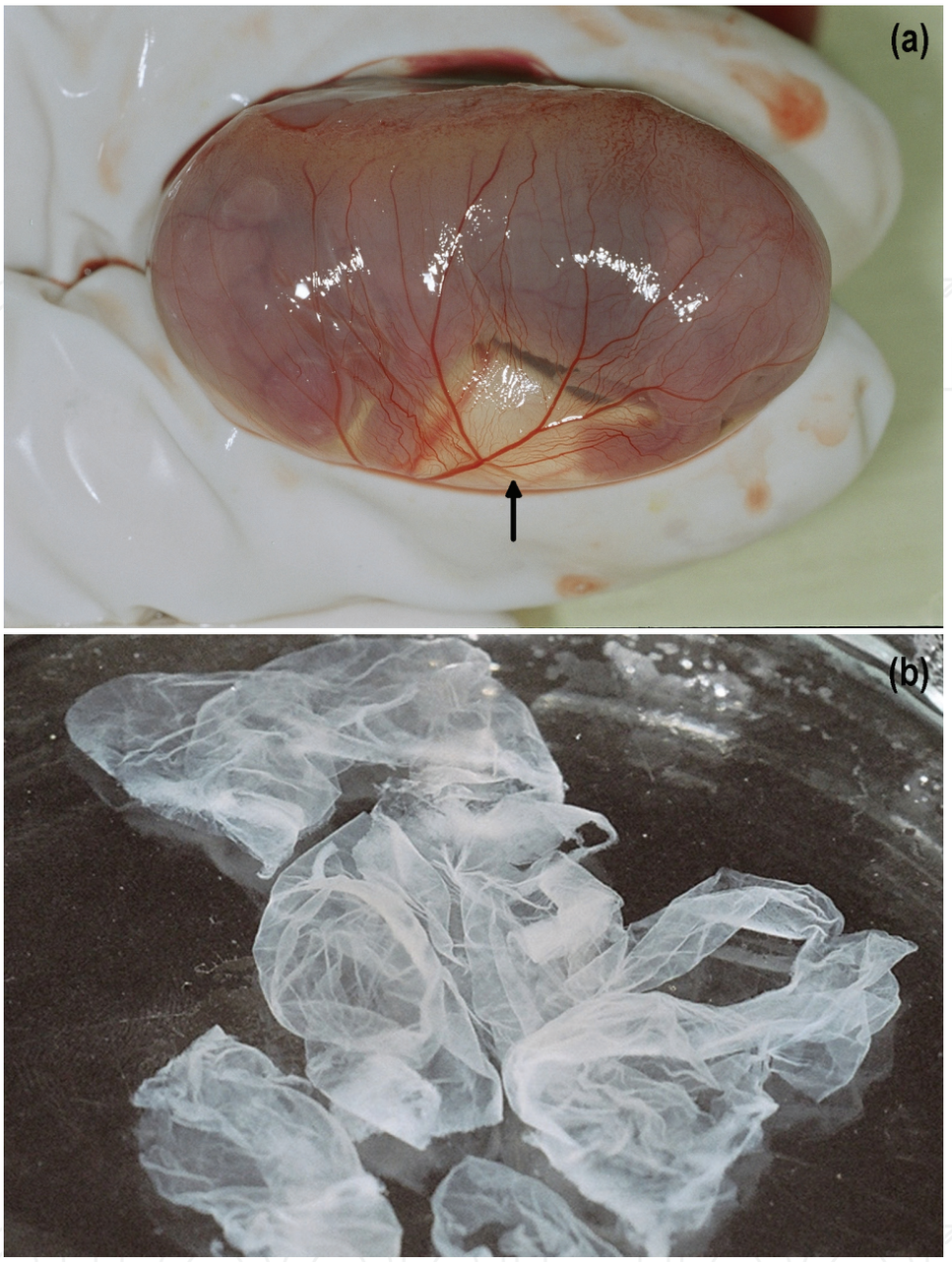

Figure 6. (a) Fetus, amniotic, and chorionic membrane (arrow) and (b) fresh HAM separated from the chorionic membrane and placed in sterile physiological saline solution and phosphate buffer at pH 7.4.

extracellular matrix of the connective tissue in the submucosa region, favoring its degradation during the healing dynamic processes. Investigations report the AM presence of fibronectin, elastin, nidogen, collagen types I, III, IV, V, and VI, elastin, and hyaluronic acid [31, 33].

4.2.2. Homogenous demineralized dentin matrix (HDDM)

Homogenous demineralized dentin matrix (HDDM) arises from tooth structure which has been widely used to stimulate bone regeneration, inducing osteoblastic differentiation and proliferation and chemotaxis. Hence, HDDM accelerates the bone repair process, increases bone mass, and improves bone quality without causing any rejection or infection. HDDM

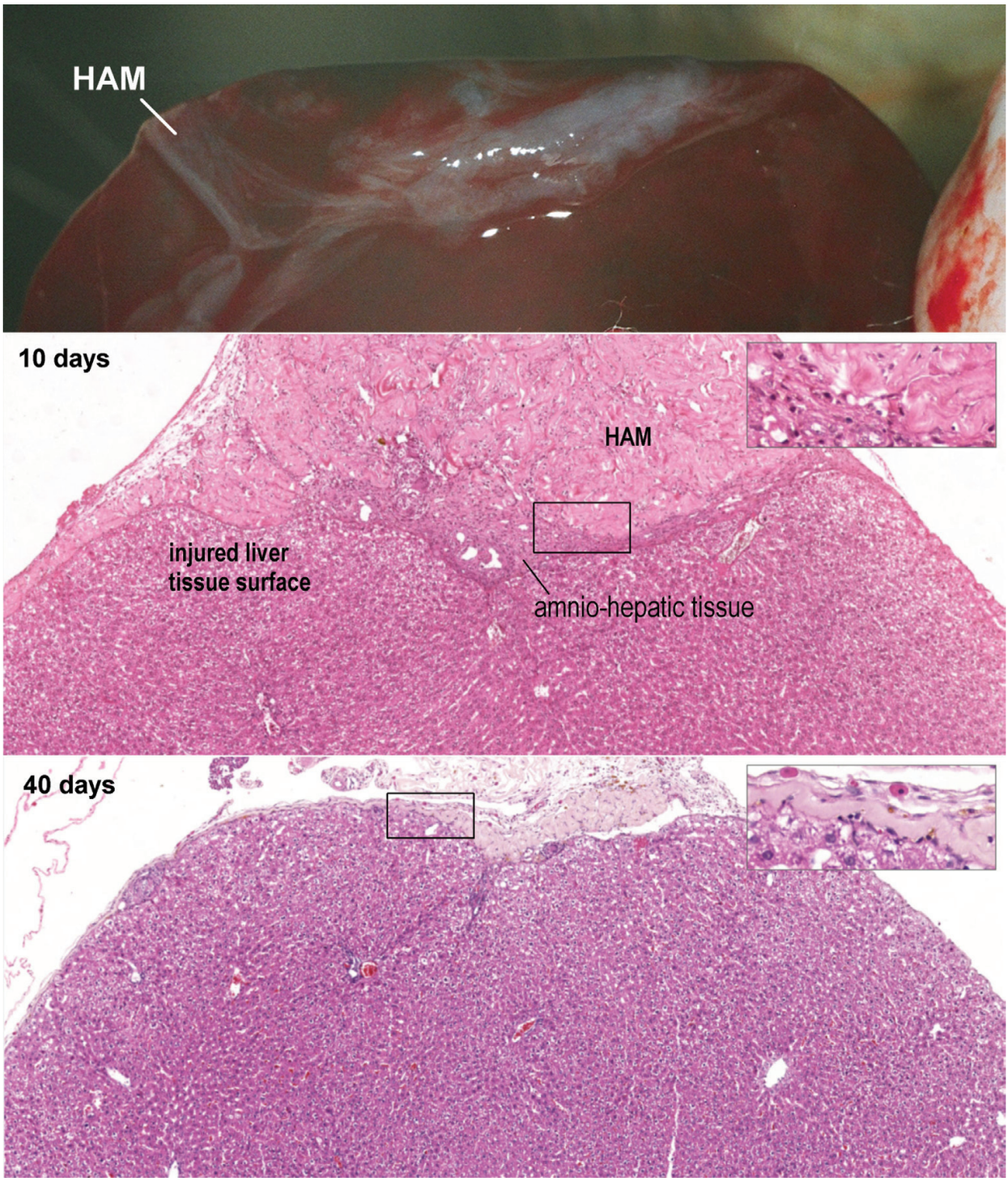

Figure 7. HAM placed on the surgically induced liver wound, HAM intimately adhered to the surface of the injured liver tissue and underwent metaplasia turning into amnion-hepatic tissue in 10 days post-surgery, and remnants of HAM on liver surface in the final step of the liver tissue regeneration in 40 days post-surgery. (hematoxylin-eosin, magnification ×25).

slices comprise an extracellular matrix rich in collagen, without vessels, and act as a reservoir for various proteins that are embedded within the matrix and are available to local cells. Regarding its main property, it is proved that the osteoinductive cascade begins with chemotaxis of bone progenitor cells, mitogenesis, angiogenesis, and bone cell differentiation. The cell recruitment, division rate, and differentiation of these cell lines are under the direct

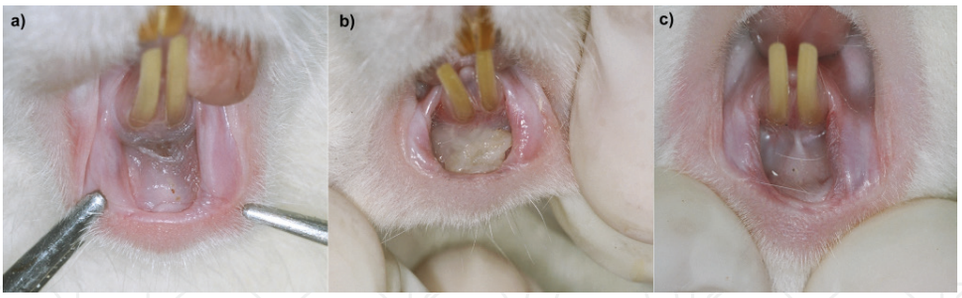

Figure 8. Oral mucositis in labial fornix region of inferior incisors (a), HAM placed on the wound (b), and normal oral mucosa surface after 7 days of treatment with HAM (c).

control of HDDM growth factors, including BMPs [11, 14, 15]. Others growth factors include TGF-β, IGF I and IGF II, PDGF, FGF, TGF-β, and VEGF [17].

HDDM slices strongly favor the chemotaxis of appropriate cells into the surgical defect, the transformation of undifferentiated mesenchymal cells into osteoprogenitor cells, osteoblast proliferation and differentiation, and the synthesis of the extracellular matrix with mineralization of osteoid tissue that leads to accelerated bone maturation and remodeling. It is worth highlighting that the HDDM slices initially yielded hemostatic effects by mechanical action after their implantation in the periphery of the defect. Furthermore, it was demonstrated that the HDDM was incorporated into the newly formed bone matrix and resorbed during the bone remodeling process. Moreover, numerous osteoblasts and osteoprogenitor cells were also located adjacent to the HDDM, confirming its strong chemotactic activity. Studies suggested that HDDM provides bioactive molecules for the host of proteins and growth factors can be released through dentin matrix degradation and exposed dentinal tubules when HDDM is used in the form of slices [6, 11, 14, 15, 17]. Furthermore, when this biomaterial is used in the periphery of surgical defect, it is able to stimulate the reconstruction of the bone architectural microstructure,

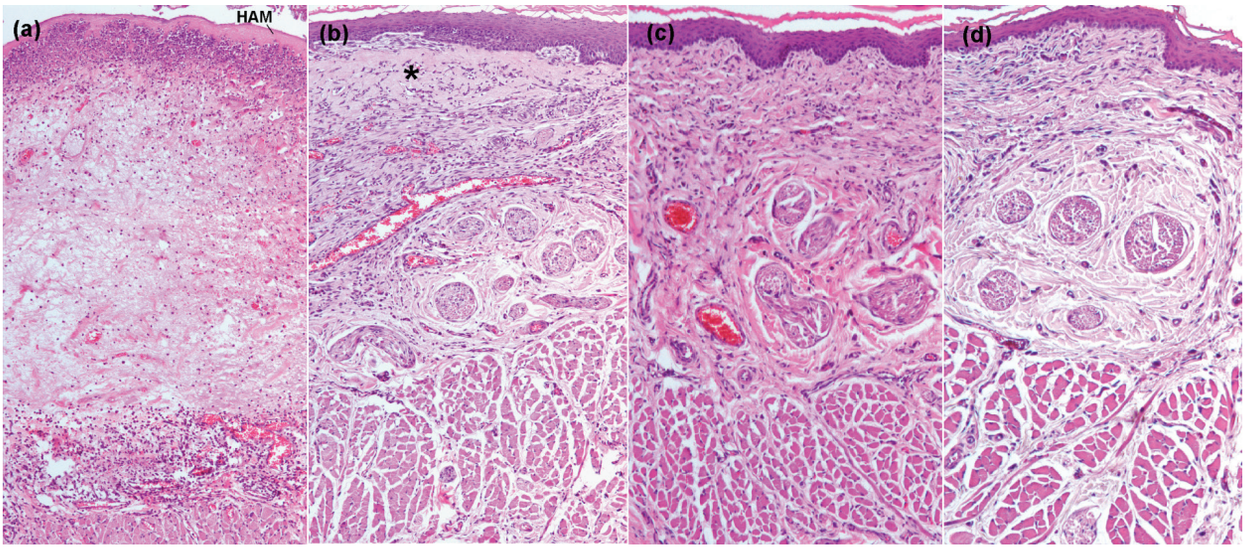

Figure 9. 5-Fluorouracil-induced oral mucosites. Histomorphological features divided into four phases: (a) inflammation (3 days), (b) cell proliferation (7 days), (c) tissue organization (14 days), and (d) tissue repair (21 days). Asterisk: HAM remnants incorporated into connective tissue in the submucosa region (proliferation phase) (hematoxylin-eosin, magnification ×25).

resulting in formation of mature bone trabeculae and bone marrow. Initially, bone trabeculae were mature at the periphery and immature at the centre of the bone defect; thus, centripetal bone growth was seen in the bone repair process (**Figures 10**, **11**). Finally, an exophytic bone growth can be evidenced due to the highest chemotactic, mitogenic, and osteogenic potential of the HDDM. Dependent of the animal's age, a physiological conversion from red to yellow bone marrow can be observed, leading to large and regular medullary spaces (**Figure 12**).

Concerning the evidence of HDDM biocompatibility, two hypotheses are suggested by the present study. First, cell surface histocompatibility antigens and sequestered antigens are absent; however, they may be present throughout the extension of the remnant odontoblastic processes within the HDDM. Second, the decalcification process for teeth could cause the denaturation of surface proteins on the plasma membrane of the odontoblastic processes. It was considered that the plasma membrane of the odontoblastic processes could present not only cell surface histocompatibility antigens, but also sequestered antigens that, when not exposed to the cells of the immune system, do not trigger immunological reactions.

The resorption process of the HDDM slices presented the following phases: (1) the dentin matrix was first incorporated into the newly formed bone tissue; (2) next, the dentin was degraded during bone remodeling; and (3) the area in which the dentin matrix was located was replaced by new bone tissue (**Figure 13**).

Therefore, the HDDM could be considered as an ideal bone graft material since it stimulates osteoblast differentiation and proliferation and potentially leads to efficient bone regeneration. We suggested that it could be used as a scaffold for stem cells and bone growth factors, since its biological properties have shown an excellent bioactive material for bone tissue engineering in diabetes.

Autogenous demineralized dentin matrix (ADDM) has been used to accelerate the dental socket wound healing process in humans. The ADDM is considerate biocompatible with surgical human dental sockets. Initially, radiopaque image suggestive of remaining ADDM slices can be found. Moreover, the radiographic bone density of the dental sockets treated with ADDM was similar to that of the surrounding normal bone from 90th day. It is worth highlighting that alveolar bone architecture is improved when the ADDM is used as an engineering tissue (**Figure 14**).

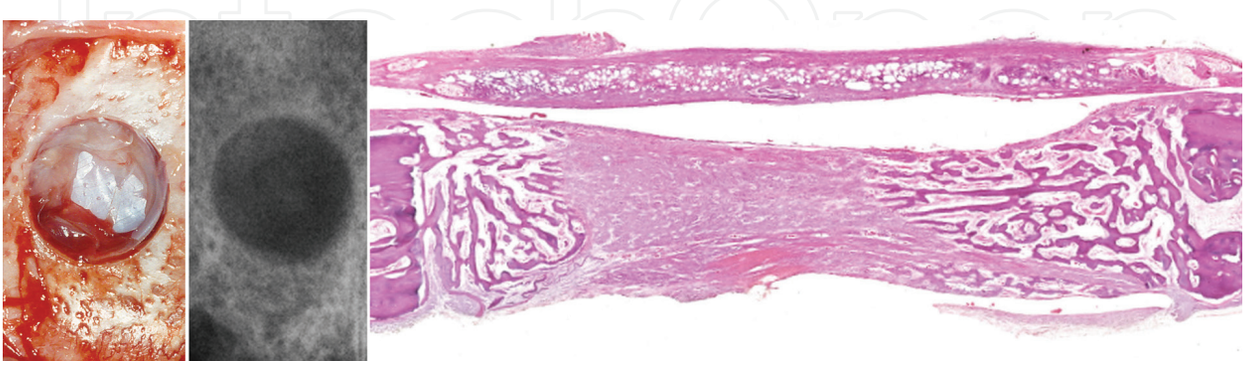

Figure 10. Clinical and radiographic images of surgical defect in the parietal bone of diabetic rabbits taken at 15 days. HDDM slices promoting hemostatic effects by mechanical action after their implantation and their osteogenic activity after 15 days in diabetic rabbit (H.E., original magnification ×25) (Source: Gomes et al. [17]).

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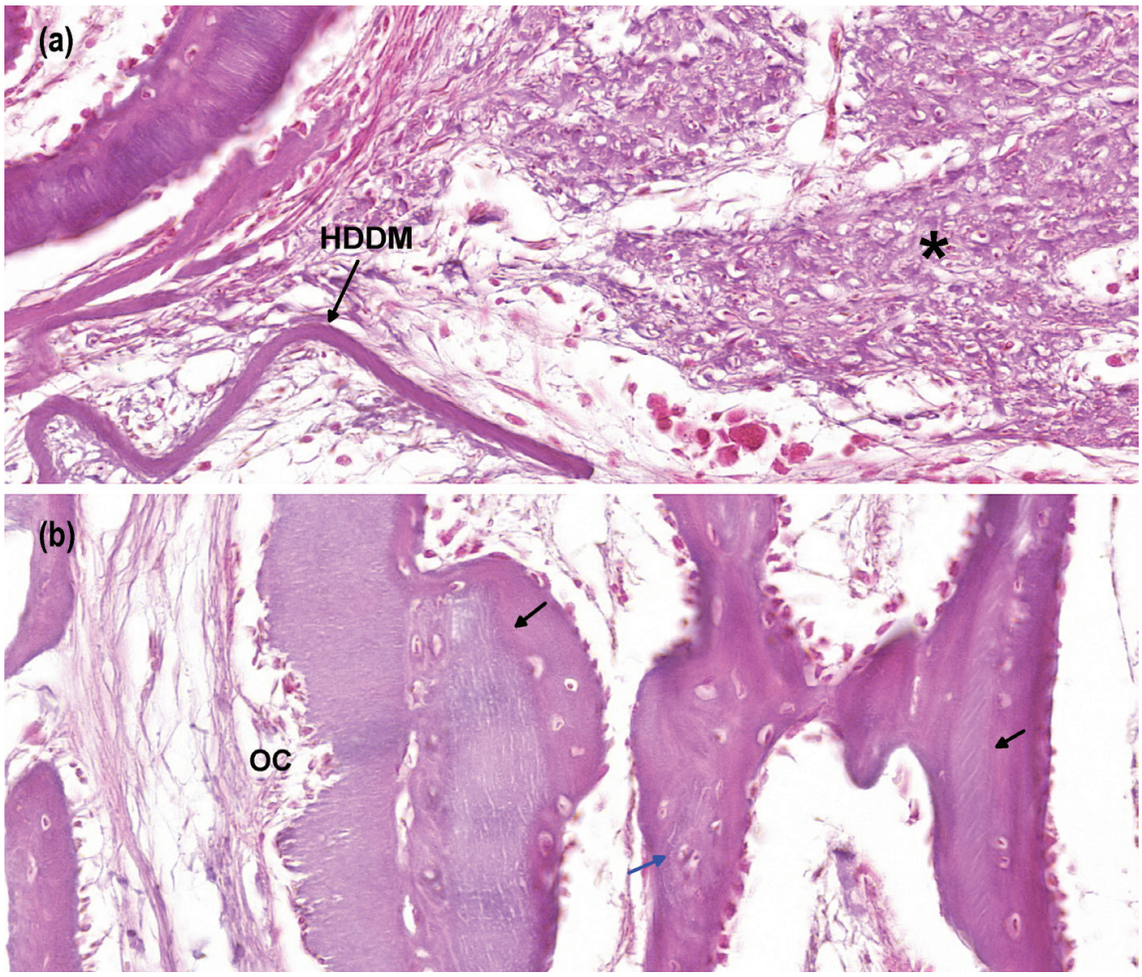

Figure 11. Performance of the HDDM inside the surgical bone defect after 15 days in diabetic rabbit: (a) intense osteogenic connective tissue showing numerous osteoblasts (asterisk) showing chemotactic activity; (b) HDDM slices in resorption process by osteoclasts (OC), resorbed HDDM slices (blue arrow), and HDDM slices incorporated into the newly formed bone tissue (black arrows) (hematoxylin-eosin, magnification ×200).

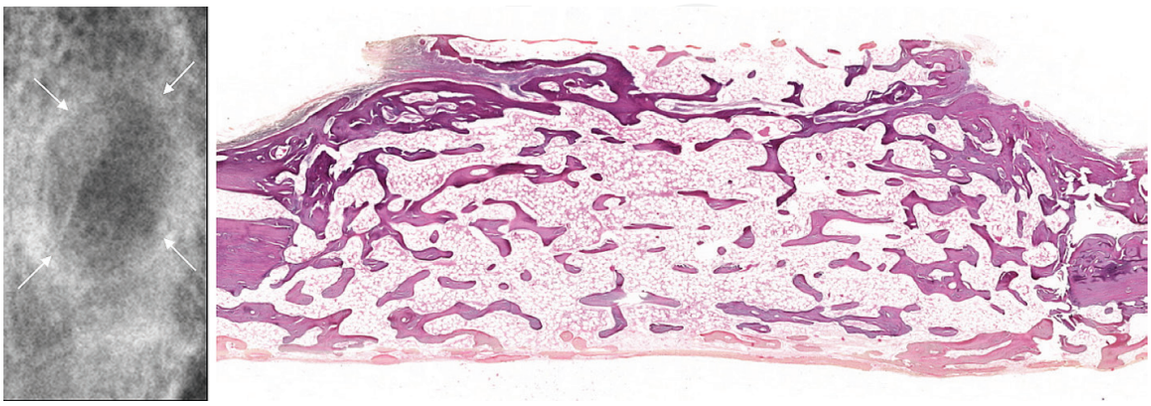

Figure 12. Radiographic image of surgical defect in the parietal bone of diabetic rabbits taken at 90 days and defect region completely filled with mature bone trabeculae a bone marrow (hematoxylin-eosin, magnification ×25) (Source: Gomes et al. [17]).

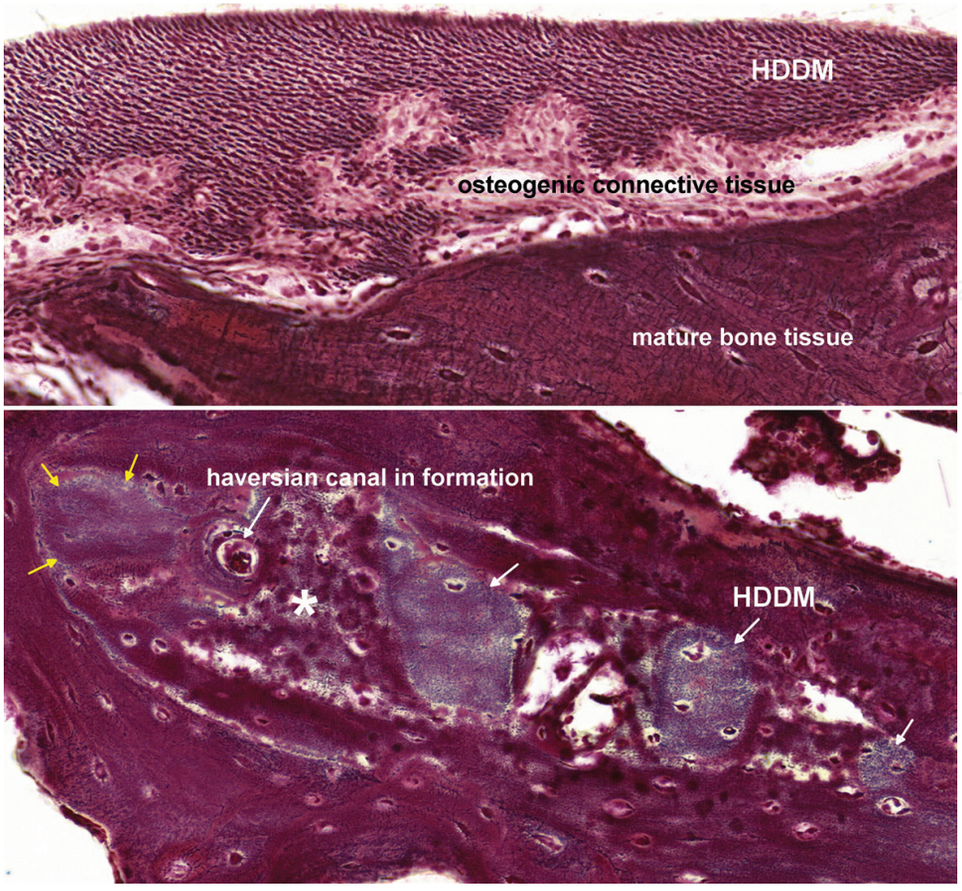

Figure 13. Surgical bone defect region after 90 days in diabetic rabbit. Phases of the HDDM degradation during the bone remodeling process: HDDM in degradation (white arrows), exchange of HDDM by well-cellularized and immature bone tissue with remnants of dentin matrix (asterisk), and replacement of the preexisting HDDM by mature bone tissue (yellow arrows) (Schmorl's stain, magnification ×200).

4.2.3. Platelet-rich plasma (PRP)

Platelet-rich plasma (PRP) has been described as a source of growth factors and a potentially ideal scaffold for tissue engineering in regenerative medicine. PRP is an autologous product that contains highly concentrated number of platelet in a small volume of plasma from whole blood by gradient density centrifugation. It is a proven source of growth factors like platelet-derived growth factor (PGDF) and transforming growth factor β1 and β2 (TGF-β1 and β2), which is obtained by sequestering and concentrating platelets by gradient density centrifugation [25, 47]. This substrate is considered to ameliorate tissue regeneration due to presence of essential various cytokines and growth factors (GFs). Among them, platelet-derived growth factor (PDGF), transforming growth factor β1 (TGF-β1), insulin-like growth factors (IGF), platelet factor 4 (PF-4), fibroblast growth factor 2 (FGF-2), vascular endothelial growth factor (VEGF), and epidermal growth factor (EGF) are considered to be the most important. Subsequently, through stimulation of vascular ingrowth, macrophages arrive and start producing their own cytokines and GFs, some similar to those produced by platelets. This results in a new and continued local tissue repair and regrowth [40]. The cytokines and growth factors also

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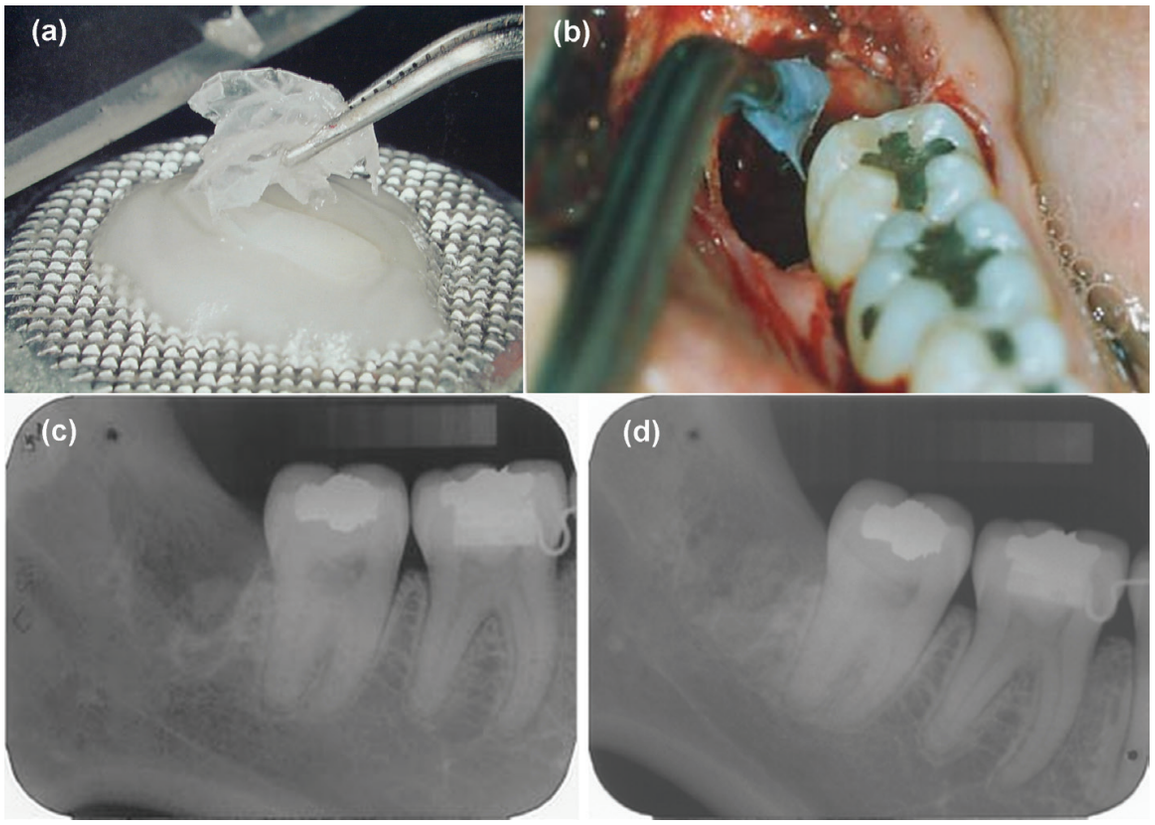

Figure 14. ADDM cut into slices with frozen microtomy (a) and placed into human dental socket covering its surface (b). Periapical radiographs after 15 (c) and 90 days (d) post-surgery. Arrow: radiopaque image suggests remaining of ADDM slices (Source: Gomes et al. [10]).

recruit resident stem cells to the site of injury, where they are stimulated to secrete additional growth factors and anti-inflammatory cytokines, causing more increase in collagen and matrix synthesis. Furthermore, the recruited stem cells will react with the environment to differentiate in parenchymal cells or replace the injured tissue [32].

Some investigators have reported that platelet-rich plasma (PRP) becomes more efficient in tissue repair when associated with bone grafts, bioactive material scaffold, or mesenchymal stem cells (MSCs) which are recruited at the wound site, accelerating tissue repair. This complex could exhibit a synergistic effect. PRP contains numerous proteins including PDGF ($\alpha\alpha$, $\beta\beta$, and $\alpha\beta$ isomers), TGF-b (β1 and β2 isomers), VEGF, angiopoietins, FGF, platelet-derived epidermal growth factor (PDEGF), epidermal growth factor (EGF), IGF, and fibronectin. When it is placed into bone surgical defect, it is quickly filled by a loose connective tissue and newly formed bone trabeculae in a linear arrangement. This connective tissue exhibits myxoid features and numerous newly formed blood vessels, showing intense angiogenic activity and stimulating the formation of bone marrow tissue. The myxoid tissue consisted of very delicate collagen fibers, numerous spindle cells, and a large amount of extracellular amorphous matrix (**Figure 15**). It is possible that the myxoid tissue and intense vascularization have occurred due to the preservation of bioactive angiogenic factors in the PRP, e.g., VEGF and angiopoietins, after its confection in laboratory [17].

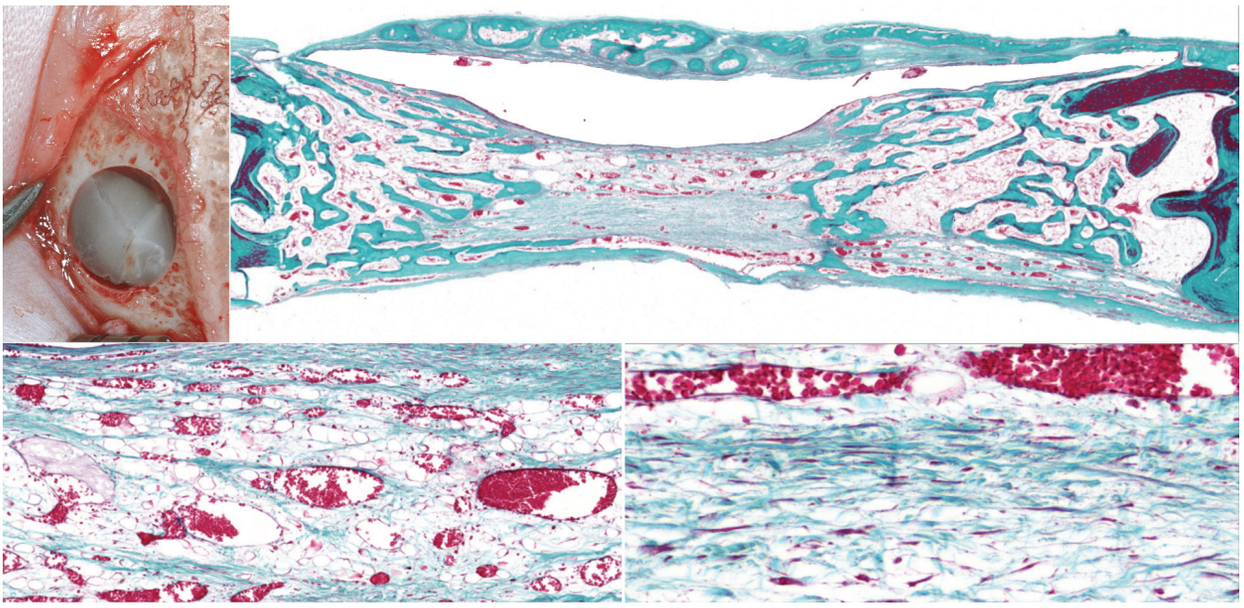

Figure 15. PRP into surgical bone defect stimulating angiogenic activity and myxoit tissue with very delicate collagen fibers, numerous spindle cells, and a large amount of extracellular amorphous matrix, in a period of 30 days (Source: Gomes et al. [17]).

4.3. Alloplastic materials

The ideal implant should be composed of material that is biocompatible, affordable, and nondegradable. Although many materials have proven suitable, alloplastic materials are an attractive implant type, in particular, for the treatment of maxillofacial deformities and for reconstruction [7, 30]. To choose an ideal alloplastic material, first, we must identify the usage needs and their biological and physical properties as biocompatibility, easy of obtaining, noncarcinogenic and nonallergenic material, few production of inflammatory response, essential predeterminant physical-chemical properties to tissue reconstruction and regeneration, no susceptible to infections, sequelae or tissue sequestrum, easy anchorage, handling and sterilization without losing your characteristics and physical structure, high porosity to promote surrounding tissue ingrowth, similar consistency to replaced tissue, stability of contact surface, and good permanence in the implanted region to allow the suitable tissue reconstruction, especially in large defects. Among the several types of available alloplastic materials, porous polyethylene (porous PTFE), hydroxyapatite, and polyurethane resin derived from castor oil implants have been widely indicated in literature. It is worth mentioning the efficient effects of the porous PTFE implant when used in hard and soft tissues. Scientific investigations have shown its application in partial or total ossicular replacement, restorative and esthetic rhinoplasty, orbital implants, ear reconstructions, and augmentation or correction of craniofacial deformities such as temporal and mandibular regions, zygomatic arch, nose, and paranasal areas [7, 8]. Clinical and experimental studies have proven that the PTFE porosity aids surrounding tissue invasion, triggering good adhesion, and stability of the implant in the host site (**Figure 16**). However, this material can be considered poorly biocompatible by tissues, especially in diabetes, due to moderate-intense infiltration of mononuclear inflammation cells as lymphocytes, macrophages, and foreign body-type multinucleated giant cells, especially in uncontrolled diabetes.

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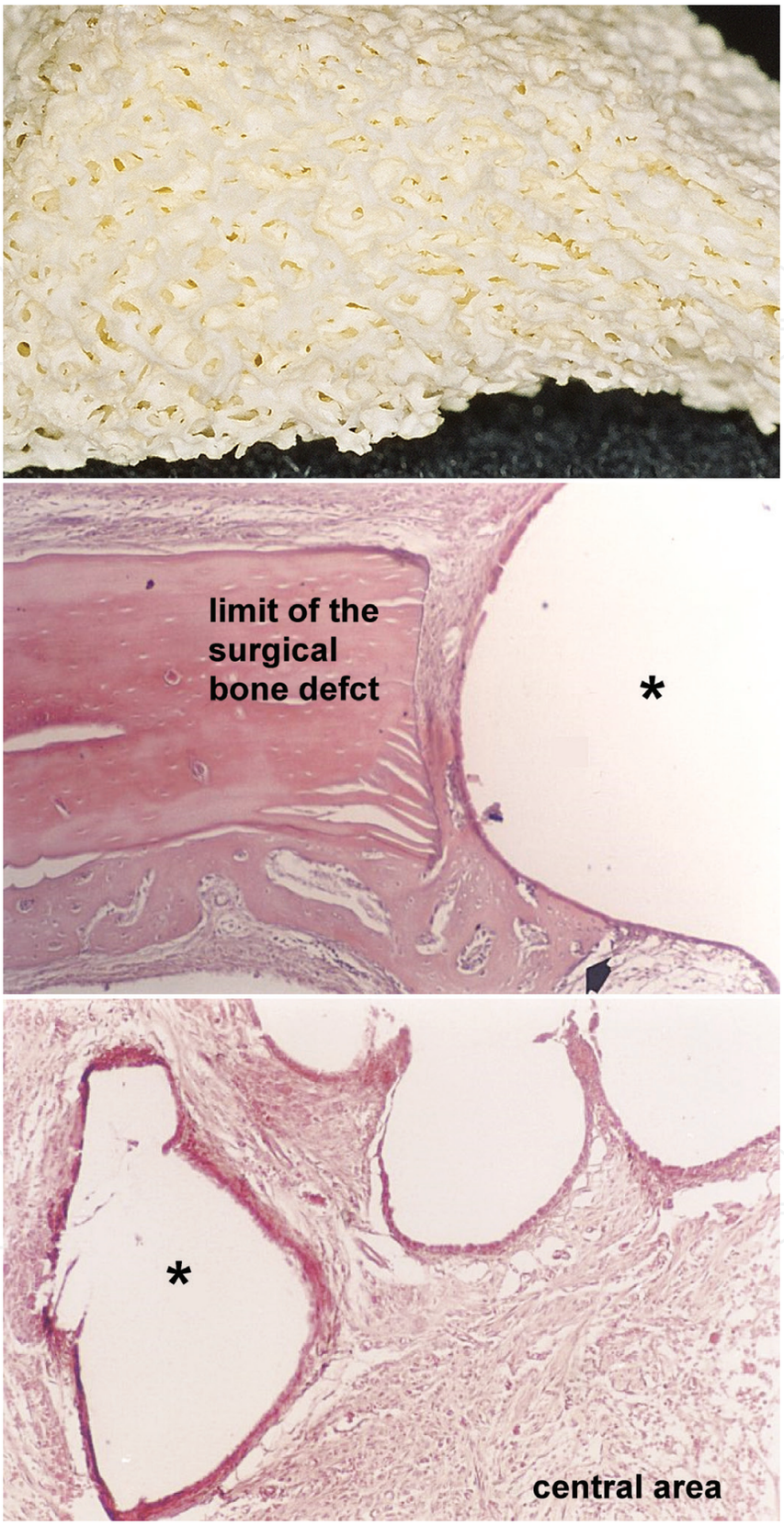

Figure 16. Porous PTFE implanted into surgical bone defect in diabetic rats after 15 days. The defect was filled by fibrous connective tissue with discrete infiltration of mononuclear inflammatory cells and few newly formed bone trabeculae (arrow). The cavities show negative images (asterisk) of the polyethylene, and the soft tissue represents the pore areas (hematoxylin-eosin, magnification ×200).

As a compensatory factor, some therapeutic drugs could be used in association with alloplastic material, such as salmon calcitonin and verapamil. Systemic administration of salmon calcitonin has been widely used in patients with pathologies that affect the bone metabolism, including osteoporosis, osteogenesis imperfect, and Paget's disease, because of its recognized ability to inhibit bone resorption [8]. For support therapy, the salmon calcitonin can be indicated to treat aggressive cherubism, promoting the inhibition of multinucleated giant cell formation and osteoclastic activity, leading to a regressive process of the disease [16].

Regarding to the verapamil, it is used for treatment of high blood pressure, cardiac arrhythmias, and pectoris angina, as well as it is often indicated for diabetic individuals. Diabetic individuals are great users of this drug. The verapamil, a potent calcium channel blocker, promotes the inhibition of voltage-dependent calcium channel, L-type, reducing the Ca^{2+} entry into the cells and, consequently, altering their functions. Osteoclast lineages are affected, resulting in the inhibition of bone resorption and, thus, favoring the new bone tissue formation.

Some researches demonstrated that the verapamil has influenced the calcium balance in the mineralized tissues. It changes the calcium trophic hormone action, altering the endocrine regulator effect in the bone turnover process, since it acts directly in the inhibition of the osteoclasts activity. On the other hand, the increase of intracellular calcium levels of osteoblast stimulates the IGF-I, IGF-II, and TGF-β production, favoring the bone tissue formation [2, 8].

In addition, implant neovascularization is essential to recruit inflammatory and progenitor cells, initiating the wound healing and/or leading to an exponential formation of new tissues [8, 17]. Thus, researches have suggested an additional bioactive material to the porous polyethylene implant, as mesenchymal stem cells (MSCs) or angiogenic and mitogenic factors, so that they can present synergistic effects and improve the environment and, consequently, the development of desirable tissues in a variety of reconstructive and restorative surgeries.

5. Considerations

Considering the exponential growth trend of chronic diseases, in particular, diabetes mellitus, ideal bioactive biomaterials for hard and soft tissue reconstruction and regeneration have been a great challenge for many researchers in worldwide. To choose an ideal biomaterial to be implanted in diabetes, we must first know the cellular and molecular pathophysiological mechanisms following immeasurable damages in the tissue response against any extrinsic factors, including impacts or grafts. In regard to the biodynamic constraints of the repair process, the recruitment of cells, as inflammatory and progenitors cells, and growth factors and cytokine production or action are largely impaired in diabetics individuals, in particular, with uncontrolled hyperglycemia. As undesirable results, these materials could increase the risk for and severity of the diabetic complications instead of favoring the tissue regeneration process.

Based on basic concepts of biomaterial, it is important to highlight that the biocompatibility, material storage without loss of viability, ease of obtaining the material, favorable cost and benefit relationship, and mainly preservation of its inductive properties must be considered as pivotal parameters for tissue-engineered implants which could be used in diabetes. Other concerns of researchers are to identify the reliable material sources that do not pose any risk

to the donor or to the individual that will receive the cells, and to accomplish the isolation of cells with high potential of expansion and proliferation.

In this regard, we discussed some property and effects of biomaterials and alloplastic materials that could surely be indicated in cell therapy and tissue engineering, especially in diabetic individuals. As a compensative factor in diabetes, we suggested the clinical application of the AM and DDM in isolation or in association with other materials commonly found in the literature. The highly effective biological properties of these scaffolds favored the development of impaired tissues through the restoring, maintaining, or improving tissue function, corroborating with the basic principles of tissue engineering. Special attention has been paid to AM due to rich amount of growth factor and MSCs in its mesenchymal stroma, playing a key role in the creation of implantable tissue. Moreover, the AM is considered a promising source since it is usually discarded after childbirth (in humans and animals); therefore, it could be used without ethical or religious troubles when collected. The use of this membrane in some centers can be submitted the same rules for the use of organ and tissue transplants; however, it is worth noting the importance to conduct strict control procedures as serological and microbiological screening of this membrane.

Acknowledgements

The funding source of the CEBAPE researches was supported by São Paulo Research Foundation, known as FAPESP (grant numbers: 1996/3203-2, 2002/03952-8, 2003/06017-0, 2004/04447-0, 2004/08656-0, and 2007/54996-9).

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