THE IMPACT OF DIABETES ON IMPLANT ORAL REHABILITATIONS: A BIBLIOMETRIC STUDY AND LITERATURE REVIEW

Felice Lorusso[1], Francesca Postiglione[2], Maurizio Delvecchio[3], Biagio Rapone[4], Antonio Scarano[5,*]
[1]Department of Medical, Oral and Biotechnological Sciences, University of Chieti-Pescara, Via dei Vestini, 31, 66100 Chieti, Italy - [2]Department of Medical, Oral and Biotechnological Sciences, University of Chieti-Pescara, Via dei Vestini, 31, 66100 Chieti, Italy

ABSTRACT

Introduction: *Diabetes represents a potential risk factor for bone healing and dental implant treatment predictability. The aim of the present investigation was to perform a bibliometric evaluation of articles on the topic of the impact of diabetes on implant oral rehabilitations.*

Material and methods*: A Boolean keyword search was performed on Scopus database and recorded the list of articles, authors and affiliations. The journal impact factor was calculated by the Journal Citation Report Clarivate electronic database. The total papers, number of citations and journal impact factors were calculated.*

Results*: a total of 476 papers and 162 authors were assessed. The mean authors total citations were 2880.11± 4070.24 and the mean impact factor value was 1.942±1.15*

Conclusions*: uncontrolled diabetes impacts on dental implant rehabilitation with an increased risk of implant failure and peri-implant disease in long-term rehabilitation.*

Keywords: *Diabetes, Dental Implant, Bibliometric study, Peri-implantitis.*

DOI: 10.19193/0393-6384_2020_6_512

Received *June 30, 2020;* ***Accepted*** *August 20, 2020*

Introduction

The osseointegrated dental implant is an effective procedure for rehabilitation of function and aesthetics of the jaws[1,2]. The success of the procedure is correlated to an intimate contact between the dental implant surface and the surrounding bone tissue[3-5]. The early bone healing of a dental implant is determined by the recruitment of osteogenic progenitors and migration to the implant surface, the generation of bone matrix and growth and finally, the remodelling processes[6-8]. The long-term adaptation, remodelling and maintaining of the bone is determined by the local physiological biomechanical and physical stimulation of the healing site, generated during the functional activity of the implant[6,9-12].

The procedure for dental implant positioning is related to a sequence of phases from osteotomy trauma, bone debris deposition, blood hemostasis and clot organization and hypoxia of the tissues[13]. The healing phases can be influenced by the immune system activity and negatively affected by the involvement of systemic pathological diseases such as diabetes, osteopenia and pharmacological therapies[14]. Moreover, other local factors can influence the healing such as implant features and surface properties[5,15,16], screw positioning insertion torque[17-19], drilling temperature[16,20-22], and micro- movements[23]. Also, the local presence of residual metal particles and ions is able to induce the release of proinflammatory factors, and osteoclast resorption activity at the level of the peri-implant tissues[24-26].

The release in the oral cavity of metals and ions such as titanium, vanadium, and aluminum by corrosion has been reported to produce inflammation and reactions at the level of peri-implant soft and hard tissues with local osteolysis[27]. Diabetes mellitus is a multi-systemic disorder that affects the regulation of blood glucose levels and it is a global impact disease[28,29]. Saeedi et al. reported that the diabetes world-wide prevalence was about 9.3% in 2019, with a non-homogeneous distribution of the population affected by the disease[30]. In fact, the prevalence rate seems to be increased in urban environments if compared to other regions, while it has been calculated that half of the affected patients do not have a diagnosis of diabetes[30]. In literature, three main classes of diabetic disease are known[30]:

• type 1: insulin-dependent or juvenile diabetes, due to autoimmune beta-cell destruction leading to progressive insulin deficiency; this accounts for 5-10% of diabetes;

• type 2 mellitus: insulin resistant or adult diabetes, due to inadequate insulin secretion, usually with insulin resistance; this accounts for 90-95% of diabetes;

• gestational diabetes: ranging from glucose intolerance to diabetes that was not present before pregnancy; the prevalence has not been estimated as it usually disappears after the pregnancy. Another uncommon type of diabetes is due to genetic causes (monogenic or syndromic diabetes), disorders of the exocrine pancreas, and drug- or chemical-induced diabetes; it accounts for < 5% of diabetes (31).

In literature, the negative effects of diabetes on oral tissue healing are related to the levels of glycemic and glycated hemoglobin (HbA1c) control and the presence of chronic micro-vascular alterations and wound infections, defects of immunity and granulocyte activity[24,32]. In literature, it was reported that high glycemic levels are correlated to an increased release and tissue accumulation of advanced glycation end products (AGEs). Moreover, the advanced glycation end products seem to be accumulated at the level of the collagenic bone matrix, proportionally with ageing[30]. In literature, it was reported that the advanced glycation end products are also able to decrease the biomechanical properties of the bone tissue, with a significantly higher prevalence of fracture events in patients affected by diabetes mellitus if compared to healthy subjects[33]. Higher levels of blood HbA1c seem to negatively influence the production, and remodelling of collagenic matrix at the level of periodontal and peri-implant soft and hard tissues[25,34]. Higher advanced glycation end products (AGEs) are also correlated to a decreased bone density, alteration of the microarchitecture, bone remodeling, vascular microdamage, and collagen matrix alteration[35]. Histologically, advanced glycation end products (AGEs) and an associated diabetic condition are able to induce a significant increase of osteocyte lacunae density and a significant lower volume of the vascular canal[30]. A reduction of vascular canal volume is related to the action of high glycemic levels in a diabetic condition that is able to alter the micro- and macro-vascular network of the bone tissue[36]. In literature, it was reported that the advanced glycation end products (AGEs) are associated to nonenzymatic glycosylation with a significant alteration of extracellular matrix that shows an increased weakness against the action of pathogens and agents. This condition is also correlated to an increased expression of proinflammatory markers and molecules and a hyper-reactive immune tissue response[30,37]. In the oral environment, these molecule produce their effects on gingiva and periodontal cell receptors and they are able to alter fibroblastic physiological activity and proliferation in oral tissues[14,33,38].

A similar negative activity has been reported for the peri-implant tissues, where chronic hyperglycemia seems to produce a significant effect on local inflammation and loss of implant supporting tissues[39]. The degree of glycaemic levels and pharmacological therapy can represent a strong influence for the post-operative healing period and complications[29]. In fact, this condition induces a functional alteration of the immune response of the site with a higher risk of infection due to a modified microbiocide activity and a decreased potential wound healing[28]. Clinically, the high glycemic level is able to induce the proliferation of several bacteria and pathogens and affects the surgical flap healing due to the diabetic microangiopathy, that could produce an impairment of the barrier of the surgery access site[32].

Peri-implant diseases are pathologies induced by bacteria biofilm characterized by chronical inflammation of hard and soft tissue with resorption of surrounding bone[23]. Peri-implant diseases are a category of pathologies that include mucositis and peri-implantitis. The absence of signs of surrounding bone loss and the inflammation of the peri-implant soft tissue is commonly associated with mucositis[30]. Moreover, the contemporary presence of resorption of supporting bone loss is associated to peri-implantitis[30]. In the literature, it has been demonstrated that diabetes and smoking habits play a crucial role for

the development and the progression of peri-implant diseases[28]. In fact, diabetes induces a decrease of wound healing potentiality, local tissue hypoxia and it inhibits the chemotaxis of the immunity cells[40]. In literature, it has been reported that hyperglycaemia shows a higher prevalence in diabetic patients with a hyperinflammation response in the periodontal tissues[29]. The pathogenesis of the periodontal AGE-related damage seems to be correlated to an increased activity of pro-inflammatory cytokines, interleukins and release of metalloproteinases[32,36,39,41]. Moreover, long-term uncontrolled high glycemic levels are able to produce important alterations of the tissue physiology, to affect the barrier function and local immunity, capable of neutralizing the periodontal agents and to alter the neutrophil chemotaxis and phagocytosis[24,29,36]. In an oral environment, these pathological modifications are able to generate a decrease of the healing processes capability of the soft and bone tissues during the implant and odontostomatological procedures[38,41]. The aim of the present investigation was to perform a bibliometric evaluation and to review the scientific production related to diabetes mellitus in implant oral rehabilitations

Materials and methods

Search Strategy

The detection of the suitable keywords for electronic database research was performed by the use of Pubmed/MeSH terms function to identify the descriptors and their synonyms that would enable us to identify the topic being studied with the maximum possible precision[42-44].

The following Bolean search equation was applied for the electronic search strategy conducted on Web of Science (SCI) and Scopus® database: (dental AND implant OR maxillary AND implant OR mandibular AND implant OR endosseous AND implant OR osseointegrated AND implant) AND diabetes). The electronic database research and data collection was performed by two expert reviewers (F.L. and A.S.) independently on June 28th 2020. The present review and bibliometric analysis was performed according to the PRISMA guidelines[45].

Inclusion Criteria

In vitro studies, review and studies, research papers, editorial letters in the English language assessing dental implant and diabetes were included in the present investigations. No limitations about publication date were applied to the research.

Publications that did not comply with the inclusion criteria were excluded from the evaluation.

Selection of the Studies

The selection of the studies was performed independently by two expert reviewers (FL, AS) and, if the abstract was not available, the full text of all eligible papers was obtained and evaluated to assess the inclusion criteria. For excluded articles, a report was performed about the reasons for exclusion.

Data extraction

The electronic search and data extraction were independently performed by two expert reviewers (FL and AS) on Web of Science (SCI) and Scopus® database. For the present investigation papers were considered in the English language; conference proceedings and book chapters were excluded in the present investigation. The papers' full-text were collected and in the case these not being available, the abstracts were evaluated. The title of the article, journal, subject area, document type, institute, country, author list, affiliations, citation counts, h-index were recorded into a specially designed calculation database (Excel, Microsoft Corporation, Redmond WA USA).

Bibliometric parameters

The bibliometric impact of the scientific production on the research topic being studied was evaluated by the analysis of contributions, authors and their affiliations, and scientific journals. The scientific production impact on the topic of diabetes in dental implant procedures was evaluated by the total count of contributions, citations amount h-index of authors and affiliations. The authors self-citations were excluded from the data evaluation.

The journal impact factor (JIF) and average JIF percentile were calculated by the Clarivate- Journal Citation Reports (JCR) database.

The authors' "Publication % Ratio" and "Publication % Ratio" were calculated by the following formula:

$$Pub\%\ ratio: \frac{Total\ authors'\ papers\ on\ topic}{Total\ authors} x\ 100 \quad (1)$$

$$Citation\ \%\ ratio: \frac{Total\ citations\ on\ authors'\ papers\ on\ topic}{Total\ authors\ citations} x\ 100 \quad (2)$$

Results

Study Population

The database search generated a total of 482 manuscript. A total of 47 papers were also included to the list by performing a manual search for a total of 529 papers retrieved. Performing a title and manuscript evaluation, 40 papers were excluded: 29 papers for language (no English language), 11 articles were out of the topic, 10 manuscripts were part of books and 3 contributions were conference proceedings. At the end of the search procedure, a total of 476 papers satisfied the inclusion criteria and were included in the bibliometric investigation.

In the present bibliometric investigation, a total of 476 papers and 162 authors were assessed: 473 final full papers and 3 articles in press for a total of 12247 citations (mean: 75.60 ± 59.4; max: 9; min: 0) (Tab. 1-2)

The authors' bibliometric characterization showed a mean total paper amount of 109.73± 96.37 (Range 436-0, IQR: 116.75), mean citations 2880.11± 4070.24 (Range 19319-1, IQR: 2857.75) (Fig. 1-2).

Research journal assessment

A total of 158 scientific journals were assessed in the present research with a mean impact factor value of 1.942±1.15 (range: 4.164-0; IRQ: 1.48) and the average JIF percentile was 83.79±18.68 (range: 96.154 -0; IRQ: 1.48).

The scientific journal with the most amount of papers was Clinical Oral Implants Research with a total of 31 papers (mean: 10.98 ±6.18; IRQ: 12).

The authors with most publications are presented in Fig. 1. The bibliometric characterization of the authors is presented in tab 1. The papers with the higher citation count are presented in Tab. 3.

The visual bibliometric countries network based on citation, bibliographic coupling, co-citation, or co-authorship relations is presented in Fig. 3 and Fig. 4.

Song, Y., affiliated to the Fourth Military Medical University of Xian in China, showed the highest number of total publications on the diabetes and dental implant topic, with a publication % ratio of 18.37% and a citation % ratio of 9.47% (Fig.1-2). Moreover, Song.Y showed the most complex and active network on paper activity on the impact of diabetes on implant oral rehabilitations. According to the bibliometric evaluation of the author list selection, Wang, H.L., affiliated to the University of Michigan School of Dentistry in United States, showed the highest amount of total papers with 436 articles, h-index 62 and a total of 14412 citations with a publication % ratio of 0.92% and a citation % ratio of 2.37%. The University of Bern in Switzerland was evidenced as the institution with the highest number of studies on the research topic with a total of 18 papers selected and 682 citations, while the Göteborgs University in Sweden was the most cited with a total of 980 citations and 6 papers. The Clinical Oral Implants Research was the journal with the highest number of documents with 31 papers, while Journal of Clinical Periodontology received the highest quantity of citations (2346) on 20 papers (Tab. 4).

The most cited article on the research topic was Consensus Report of the Sixth European Workshop on Periodontology published on Journal of Clinical Periodontology in 2008 by Lindhe, J. et al (Tab. 3).

Discussion

Diabetes is a risk factor for bone healing and thus, predictability, dental implant treatment, prompting researchers to evaluate the results of odontostomatological procedures. Type 1 diabetes mellitus (T1DM) is associated with decreased bone mass and microarchitectural bone alterations[25]. On the other hand, patients with type 2 diabetes mellitus exhibit normal to high bone mineral density and present an increased risk of fractures[46]. In type 1 diabetes, the bone can be affected from the diagnosis, even in childhood, leading to reduced peak of bone mass and growth impairment, with risk of osteoporosis and fractures later in life.

In type 2 diabetes, the reduced levels of bone turnover markers observed in the circulation, suggest that the activity of the bone cells is altered, even if the underlying mechanisms of the skeletal outcomes are still unclear. Some underlying mechanisms have been reported to account for bone metabolism impairment. The most important seem to be vitamin D deficiency[47] and poor glycemic control, impairing the response of bone cells to Vitamin D3[48]. In literature it was reported that in patients affected by type 2 diabetes with obesity, a higher prevalence of decreased vitamin D levels are present in younger and adult patients[47]. The vitamin D decrease has been reported as a potential critical factor for diabetes mellitus. In fact, in literature it was reported that the metabolites of vitamin D seem to influence the regulation of glucose tolerance, insulin sensitivity, glucose homeostasis[46].

Authors	Affiliations	Total Papers	H-Index	Total Citations	Topic Papers	Topic Citations	Publ. %Ratio	Cit. %Ratio
Song, Y.	The Fourth Military Medical University, Xian, China	49	14	528	9	50	18.37	9.47
Abduljabbar, T.	King Saud University, Riyadh, Saudi Arabia	96	14	649	8	50	8.33	7.70
Javed, F.	Eastman Institute for Oral Health, Rochester, United States	220	32	3632	7	254	3.18	6.99
Quirynen, M.	KU Leuven, Leuven, Belgium	268	66	13899	7	825	2.61	5.94
Fiorellini, J.P.	University of Pennsylvania, Philadelphia, United States	89	33	5587	6	402	6.74	7.20
Garrett, N.R.	The UCLA School of Dentistry, Los Angeles, United States	66	21	1538	6	253	9.09	16.45
Hamada, M.O.	University of California, Los Angeles, Los Angeles, United States	11	7	270	6	253	54.55	93.70
Kapur, K.K.	Division of Advanced Prosthodontics, Biomaterials and Hospital Dentistry, Los Angeles, United	84	26	1970	6	253	7.14	12.84
Oates, T.W.	University of Maryland Dental School, Baltimore, United States	132	32	4252	6	199	4.55	4.68
Roumanas, E.D.	The UCLA School of Dentistry, Los Angeles, United States	42	21	1369	6	253	14.29	18.48
Vohra, F.	King Saud University, Riyadh, Saudi Arabia	143	18	1035	6	51	4.20	4.93
Zhang, S.	The Fourth Military Medical University, Xi'an, China	14	3	13	6	10	42.86	76.92
Al Amri, M.D.	King Saud University, Riyadh, Saudi Arabia	37	10	300	5	92	13.51	30.67
Al-Aali, K.A.	Princess Nourah bint Abdulrahman University, Riyadh, Saudi Arabia	27	6	94	5	23	18.52	24.47
Al-Kheraif, A.A.	King Saud University College of Applied Medical Sciences, Riyadh, Saudi Arabia	116	18	1034	5	89	4.31	8.61
Alrabiah, M.	King Saud University, Riyadh, Saudi Arabia	20	5	74	5	23	25.00	31.08
Diener, R.M.	VA Greater Los Angeles Healthcare System, Los Angeles, United States	10	6	247	5	240	50.00	97.17
Duarte, P.M.	University of Florida, Gainesville, United States	123	33	3132	5	64	4.07	2.04
Lauritano, D.	University of Milano - Bicocca, Milan, Italy	216	30	2795	5	81	2.31	2.90
Song, Y.L.	The Fourth Military Medical University, Xi'an, China	49	14	529	5	50	10.20	9.45
Van Steenberghe, D.	KU Leuven, 3000 Leuven, Belgium	321	79	19319	5	711	1.56	3.68
Wei, H.	The Fourth Military Medical University, Xi'an, China	10	6	66	5	17	50.00	25.76
Bissada, N.F.	Case Western Reserve University, Cleveland, United States	154	33	3509	4	55	2.60	1.57
Castellanos-Cosano, L.	University of Seville, Sevilla, Spain	39	11	427	4	18	10.26	4.22
Freymiller, E.	University of California, Los Angeles, Los Angeles, United States	50	22	1541	4	219	8.00	14.21
Han, T.	University of California, Los Angeles, Los Angeles, United States	22	16	1593	4	219	18.18	13.75
Karimbux, N.Y.	Tufts University School of Dental Medicine, Boston, United States	154	26	2823	4	252	2.60	8.93
Kuchler, U.	Medizinische Universitat Wien, Vienna, Austria	26	13	473	4	45	15.38	9.51
Levin, L.	Medizinische Universitat Wien, Vienna, Austria	248	34	3496	4	243	1.61	6.95
Levin, S.	David Geffen School of Medicine at UCLA, Los Angeles, United States	102	30	3276	4	219	3.92	6.68
Li, D.H.	The Fourth Military Medical University, Xi'an, China	69	18	959	4	76	5.80	7.92
Liu, H.	General Hospital of People's Liberation Army, Beijing, China	181	20	1366	4	42	2.21	3.07
Liu, Z.	Yantai Stomatological Hospital, Yantai, China	42	10	241	4	25	9.52	10.37
Maló, P.	Maló Clinic, Lisbon, Portugal	72	24	2512	4	35	5.56	1.39
Marcantonio, E.	UNESP-Universidade Estadual Paulista, Sao Paulo, Brazil	171	34	3080	4	133	2.34	4.32
Mombelli, A.	Université de Genève, Geneva, Switzerland	172	51	8946	4	363	2.33	4.06
Nevins, M.L.	Private Practice, Boston, United States	81	31	3457	4	338	4.94	9.78
Romanos, G.E.	Stony Brook University, Stony Brook, United States	302	43	6555	4	244	1.32	3.72
Tangl, S.	Medizinische Universitat Wien, Vienna, Austria	70	22	1764	4	20	5.71	1.13
Torres-Lagares, D.	University of Seville, Sevilla, Spain	164	19	1295	4	18	2.44	1.39
Wang, F.	Shanghai Jiao Tong University, Shanghai, China	40	12	435	4	100	10.00	22.99
Wang, H.L.	University of Michigan School of Dentistry, Ann Arbor, United States	436	62	14412	4	341	0.92	2.37
Zhou, W.	Yantai Stomatological Hospital, Yantai, China	18	6	107	4	25	22.22	23.36
de Araújo Nobre, M.	Maló Clinic, Lisbon, Portugal	72	21	2126	4	35	5.56	1.65

Table 1: Bibliometric evaluation of the most productive authors on the research topic compared to their total paper production.

Institutions	Countries	Articles	Citations
University of Bern	Switzerland	18	682
King Saud University	Saudi Arabia	17	174
The Fourth Military Medical University	China	15	162
University of Texas Health Science Center at San Antonio	United States	14	410
Eastman Institute for Oral Health	United States	9	315
University of California, Los Angeles	United States	9	775
UNESP-Universidade Estadual Paulista	Brazil	8	147
Medizinische Universitat Wien	Austria	8	68
VA Medical Center	United States	8	581
KU Leuven	Belgium	8	855
University of Rochester	United States	8	309
Harvard School of Dental Medicine	United States	6	412
The University of Hong Kong	China	6	308
Karolinska Institutet	Sweden	6	463
Göteborgs Universitet	Sweden	6	980
The UCLA School of Dentistry	United States	6	593
University of Michigan, Ann Arbor	United States	6	193
Stony Brook University	United States	6	99
University of Seville	Spain	6	24
Xijing Hospital	China	6	111
Case Western Reserve University	United States	5	72
King Abdulaziz University	Saudi Arabia	5	19
Columbia University College of Dental Medicine	United States	5	60
Goethe-Universität Frankfurt am Main	Germany	5	129
Universidade de Sao Paulo - USP	Brazil	5	98
University of Milano - Bicocca	Italy	5	81
King Saud University College of Applied Medical Sciences	Saudi Arabia	5	90
University of Washington, Seattle	United States	5	157
University of Ferrara	Italy	5	81
The University of Sydney	Australia	5	76
Universidad de Granada	Spain	5	121
Universidade Guarulhos	Brazil	5	64
Shanghai Ninth People's Hospital, Shanghai JiaoTong University School of Medicine	China	5	101
Princess Nourah bint Abdulrahman University	Saudi Arabia	5	23
Departement Beeldvorming & Pathologie	Belgium	5	699
Yantai Stomatological Hospital	China	4	25
University of G. d'Annunzio Chieti and Pescara	Italy	4	44
Tel Aviv University	Israel	4	247
University of Groningen, University Medical Center Groningen	Netherlands	4	99
Università Vita-Salute San Raffaele	Italy	4	23

Table 2: Institutional paper production activity on the research topic.

The vitamin D metabolites also induce the inhibition of inflammation, insulin release and higher insulin resistance[40]. Another mechanism of action of the metabolites is that these molecules are able to decrease the incidence and protect the bone tissue from osteopenia in patients affected by diabetes mellitus. The vitamin D metabolites seem to produce positive influence on diabetic patients and attenuate the negative effects on AGEs[47]. The molecular mechanisms of the decrease of vitamin D levels in type 2 diabetes is not completely clarified. The association seems to be influenced by several factors ethnicity, geography, bone mass index and patients' age[47].

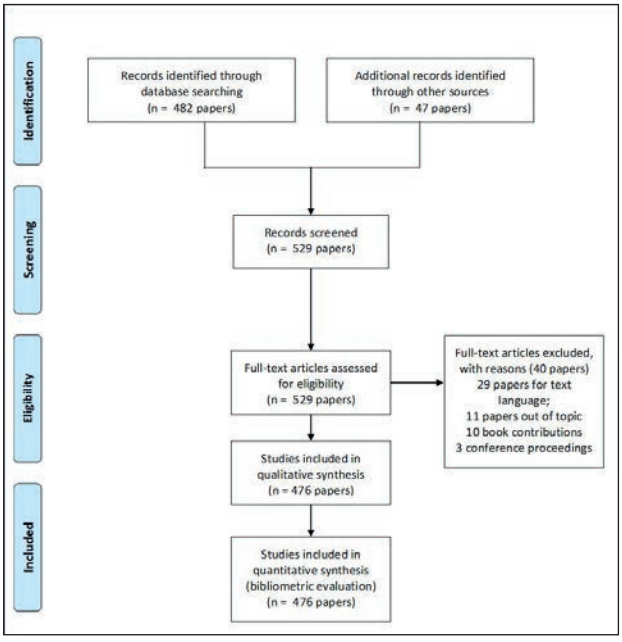

Fig. 1: Flowchart of the study selection process according to PRISMA guidelines.

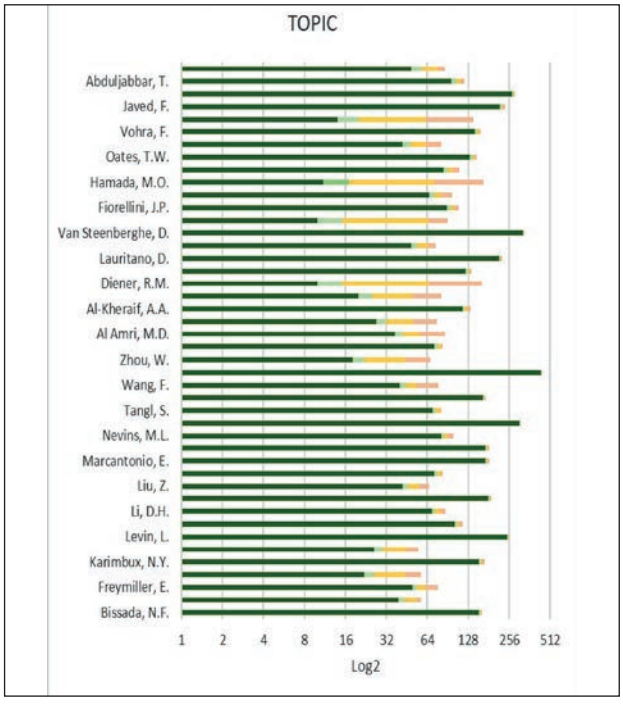

Fig. 2: Summary graph of the most productive authors: the total paper production, on topic articles, Pub%Ratio and Cit.%Ratio was calculated.

The impairment of bone metabolism is suggested by the high levels of sclerostin and Dickkopf-1, both in type 1 and type 2 diabetes[49-54]. The sclerostin protein is a molecule released in osteocytes line cells and is a key factor for bone homeostasis. In fact, the binding of sclerostin to its receptor is able to induce a signaling process that induces and inhibits new bone formation by osteoblastic line cells[50].

TOP CITED TOPIC ARTICLE	CITATIONS	PAPER TYPE
Lindhe, J., Meyle, J. Peri-implant diseases: Consensus Report of the Sixth European Workshop on Periodontology (2008) Journal of Clinical Periodontology, 35 (SUPPL. 8), pp. 282-285.	739	Consensus Paper
Heitz-Mayfield, L.J.A. Peri-implant diseases: Diagnosis and risk indicators (2008) Journal of Clinical Periodontology, 35 (SUPPL. 8), pp. 292-304.	479	Review Paper
Moy, P.K., Medina, D., Shetty, V., Aghaloo, T.L. Dental implant failure rates and associated risk factors (2005) International Journal of Oral and Maxillofacial Implants, 20 (4), pp. 569-577.	362	Research Paper
Alsaadi, G., Quirynen, M., Komárek, A., Van Steenberghe, D. Impact of local and systemic factors on the incidence of oral implant failures, up to abutment connection (2007) Journal of Clinical Periodontology, 34 (7), pp. 610-617.	230	Research Paper
Ferreira, S.D., Silva, G.L.M., Cortelli, J.R., Costa, J.E., Costa, F.O. Prevalence and risk variables for peri-implant disease in Brazilian subjects (2006) Journal of Clinical Periodontology, 33 (12), pp. 929-935.	229	Research Paper
Rosen, P., Clem, D., Cochran, D., Froum, S., McAllister, B., Renvert, S., Wang, H.-L. Peri-implant mucositis and peri-implantitis: A current understanding of their diagnoses and clinical implications (2013) Journal of Periodontology, 84 (4), pp. 436-443.	199	Review Paper
Van Steenberghe, D., Jacobs, R., Desnyder, M., Maffei, G., Quirynen, M. The relative impact of local and endogenous patient-related factors on implant failure up to the abutment stage (2002) Clinical Oral Implants Research, 13 (6), pp. 617-622.	172	Research Paper
Javed, F., Romanos, G.E. Impact of diabetes mellitus and glycemic control on the osseointegration of dental implants: A systematic literature review (2009) Journal of Periodontology, 80 (11), pp. 1719-1730.	171	Review Paper
Thomas, M.V., Puleo, D.A. Infection, inflammation, and bone regeneration: A paradoxical relationship (2011) Journal of Dental Research, 90 (9), pp. 1052-1061.	157	Review Paper
Alsaadi, G., Quirynen, M., Komárek, A., Van Steenberghe, D. Impact of local and systemic factors on the incidence of late oral implant loss (2008) Clinical Oral Implants Research, 19 (7), pp. 670-676.	152	Research Paper
Bornstein, M.M., Cionca, N., Mombelli, A. Systemic conditions and treatments as risks for implant therapy (2009) International Journal of Oral and Maxillofacial Implants, 24, pp. 12-27.	150	Review Paper
Morris, H.F., Ochi, S., Winkler, S. Implant survival in patients with type 2 diabetes: placement to 36 months. (2000) Annals of periodontology / the American Academy of Periodontology, 5 (1), pp. 157-165.	147	Research Paper
Klokkevold, P.R., Han, T.J. How do smoking, diabetes, and periodontitis affect outcomes of implant treatment? (2007) International Journal of Oral and Maxillofacial Implants, 22, pp. 173-202.	142	Review Paper
Nordberg, G.F., Fowler, B.A., Nordberg, M. Handbook on the Toxicology of Metals: Fourth Edition (2014) Handbook on the Toxicology of Metals: Fourth Edition, 1, pp. 1-1385.	141	Book Chapter
Salvi, G.E., Carollo-Bittel, B., Lang, N.P. Effects of diabetes mellitus on periodontal and peri-implant conditions: Update on associations and risks (2008) Journal of Clinical Periodontology, 35 (SUPPL. 8), pp. 398-409.	140	Review Paper

Tab. 3: Most cited articles on the research topic.

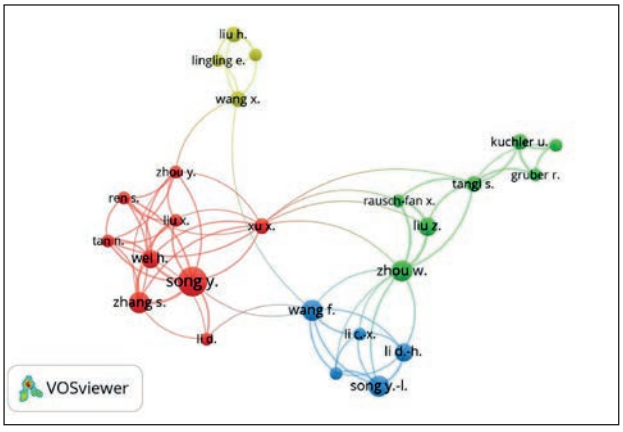

Fig. 3: Network activity on the impact of diabetes on implant oral rehabilitations.

In literature it was reported that, high glycemic levels are able to induce an inhibition of the differentiation of osteoblasts and an alteration of the parathyroid hormone activity. Consequently, these events induce a modification of the calcium and phosphorus ion homeostasis with negative effects on the bone matrix formation and osteoid apposition[24,40]. Regarding dental implant implantation, diabetes is able to induce a decreased bone remodelling activity and poorer mineralization with a slower osseointegration of the implant screw and lower bone-implant contact in diabetics.

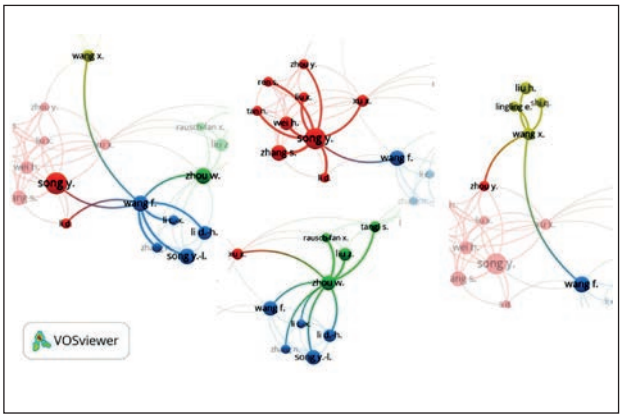

Fig. 4: Network activity of each representative author on the impact of diabetes on implant oral rehabilitations.

In the present investigation and characterization of the most cited papers, the University of Berna showed the most intense mono-institutional activity on diabetes mellitus on implant oral rehabilitations.

Moreover, the tracking of the spread of literature about the topic, and data showed that the largest activity is from China, which showed a structured and elaborated network between different nuclei research teams. This is confirmed by the evaluation of the most productive authors and institutions regarding the present research topic and the network, while Song Y. of the Fourth Military Medical University, Xian in China is the author with the most documents on the topic.

Scientific journals	Articles	Citations	IF (2018)	Average JIF percentile
Clinical Oral Implants Research	31	1431	3.825	89.09
International Journal Of Oral And Maxillofacial Implants	28	1416	1.734	56.593
Implant Dentistry	24	1060	1.214	23.626
Journal of Periodontology	21	977	2.768	85.165
Journal of Clinical Periodontology	20	2346	4.164	96.154
Clinical Implant Dentistry And Related Research	14	115	3.212	89.56
Journal of Oral And Maxillofacial Surgery	13	369	1.781	58.791
Journal of Oral Implantology	13	146	1.062	17.033
Periodontology 2000	12	246	1.062	17.033
International Journal of Oral and Maxillofacial Surgery	10	128	1.961	61.254
Medicina Oral Patologia Oral Y Cirugia Bucal	10	197	1.284	42.593
Journal of Contemporary Dental Practice	8	36	0	0
Journal of Prosthetic Dentistry	8	442	2.787	86.264
Quintessence International	6	155	1.392	33.516
Implantologie	5	2	0.074	0.549
Journal of the American Dental Association	5	60	2.572	79.67
European Journal of Oral Implantology	4	70	2.513	78.571
Journal of Biological Regulators and Homeostatic Agents	4	47	1.558	16.353

Table 4: Institutional papers production activity on the trend topic.

Diabetes is a common endocrine disease that could produce a negative effect on repair processes and wound healing, with a decrease of grow factors and local release of platelet-derived growth factor (PDGF)[55-57]. Davies et al. reported that PDGF provide a mitogenic and chemiotaxis activity for the fibroblast cell line, and osteoblasts. Moreover, PDGF seems to produce a stimulation of bone marrow-derived progenitors for differentiation and proliferation. PDGF is released with transforming growth factor beta (TGF-beta), arachidonic acid, serotonin and histamine[6]. Also, an increased interleukin-6, nuclear factor kappa-light-chain-enhancer of activated B cells 1, and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma expression have been proposed by Yu et al in the crevicular fluids and the authors suggested them as top molecular candidates for peri-implant tissue damage with type 2 diabetes mellitus[20]. The nuclear factor kappa-light-chain-enhancer of activated B cells 1 has been described as a factor that is involved with the pathway activation of the nuclear-factor kappa beta, a molecule signaling related with type 2 diabetes[58]. The interleukin-6 and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma has been described as pro-inflammatory molecules able to induce insulin resistance[59,60]. Moreover, Morris et al. reported that the disease seems to produce an increase of risk of dental implant failure if compared to non-diabetic patients[14]. Uncontrolled diabetes is able to influence the bone-to-implant contact, that seems to histologically decrease with time in several animal studies[56,61,62]. Javed et al. reported that hyperglicemia reduces the osteoblast differentiation and proliferation in favor of osteoclastic activity, increases the IL-1beta, IL-6, IL-8 and TNF-alfa and prostaglandins PGE2 release[37]. These factors reduce the new bone formation in favor of an osseous resorption activity[37,63].

The administration of antiseptic mouthrinses and an accurate oral hygiene maintenance is able to increase the prognosis of dental implant rehabilitation in diabetic patients[64,65]. Also, the preoperative administration of antibiotic drugs seems to increase the survival rate of implants by 10.5% in diabetics[14]. Lindhe et al. reported that diabetes is an important risk indicator for peri-implant disease with poor oral hygiene, a history of periodontitis, and smoking[66]. In literature it was reported that a poor metabolic and glycemic control of diabetes was related to an increase of the risk of peri-implant diseases and late dental implant failure. Peri-implant disease is a bacteria-related pathology that includes peri-implant mucositis, which represents a pathological inflammatory affection of the superficial mucosa, while the peri-implantitis is associated with a resorption of the peri-implant bone[32,64,67,68].

De Morajs et al., reported that insulin drug administration seems to produce a positive effect on the bone density around osseointegrated implants with diabetes mellitus[69]. In fact, insulin pharmacological therapy showed a higher maintenance of bone density in diabetic rats.

Moreover, the authors reported that a significant lower BIC level was observed in the insulin-treated samples if compared to non-diabetic animals[69]. In literature, it was reported that insulin is able to stabilize the glucose level and normal modulation of skeletal homeostasis[69,70]. The hormone is able to induce the deposition of bone matrix by osteoblast cells similar to insulin growth factor-1 (IGF-1), with a documented activity on the synthesis of collagenic and non-collagenic molecules[37].

Few studies focalized on the effects of a pre-diabetic condition, also known as obese-insulin resistance, on dental implant rehabilitations, while this condition is clinically characterized by hyperinsulinemia and euglycemia, and more randomized clinical trials are recommended to clarify this particular condition[71]. Obesity is clinically associated to a higher fatty diet that is able to produce an increased pheripheral insulin resistance, a decreased signaling activity on osteoblast line cells by insulin receptor (IR), insulin receptor substrate-1 (IRS-1) and protein kinase B (PKB/Akt)[72]. Moreover, the condition pre-diabetic disease is associated with a low grade chronic inflammation, with an increased macrophage activity and altered proinflammatory interleukin release such as tumor necrosis factor, IL-6 and IL-1[72]. n fact, in literature it was reported that obesity is able to induce flogosis of surrounding natural teeth and a more severe periodontal disease associated with an increased alveolar bone resorption[71]. Moreover, obesity is associated with a significantly higher probing score (BOP) and an increased peri-implant probing depth if compared to healthy patients. A higher expression of IL-1 beta and IL6 expression has been reported in patients affected by pre-diabetic condition[72]. In literature, it was reported that advanced glycation end products (AGE) are released also in peri implant crevicular fluid; moreover, these molecules are significantly increased in patients affected by pre-diabetic condition (71). The release of advanced glycation end products (AGE) seems to be significantly correlated to the flogistic response and local inflammation at the level of the peri-implant surrounding tissue[72].

Conclusions

In conclusion, the database search showed a strong interest for the topic with an intense activity of the scientific production on the research topic. The selected papers characterization showed that an accumulation of low metabolic control, microangiopathy and advanced glycation end products could be related to a lower predictability of dental implant rehabilitation that could represent a potential contraindication for implantology procedures.

References

1) Albrektsson T, Lekholm U. Osseointegration: current state of the art. Dent Clin North Am. 1989 Oct; 33(4): 537-54.
2) Nevins M, Camelo M, Koo S, Lazzara RJ, Kim DM. Human histologic assessment of a platform-switched osseointegrated dental implant. Int J Periodontics Restorative Dent. 2014; 34 Suppl 3: s71-73.
3) Piattelli A, Corigliano M, Scarano A, Quaranta M. Bone reactions to early occlusal loading of two-stage titanium plasma-sprayed implants: a pilot study in monkeys. Int J Periodontics Restorative Dent. 1997 Apr; 17(2): 162-9.
4) Scarano A, Crocetta E, Quaranta A, Lorusso F. Influence of the Thermal Treatment to Address a Better Osseointegration of Ti6Al4V Dental Implants: Histological and Histomorphometrical Study in a Rabbit Model. Biomed Res Int. 2018; 2018: 2349698.
5) Scarano A, Piattelli A, Quaranta A, Lorusso F. Bone Response to Two Dental Implants with Different Sandblasted/Acid-Etched Implant Surfaces: A Histological and Histomorphometrical Study in Rabbits. Biomed Res Int. 2017; 2017: 8724951.
6) Davies JE. Understanding peri-implant endosseous healing. J Dent Educ. 2003 Aug; 67(8): 932-49.
7) Inchingolo F, Ballini A, Cagiano R, Inchingolo AD, Serafini M, De MB, et al. Immediately loaded dental implants bioactivated with platelet-rich plasma (PRP) placed in maxillary and mandibular region. La Clinica terapeutica. 2015; 166(3): e146-52.
8) Scarano A, Crincoli V, Di Benedetto A, Cozzolino V, Lorusso F, Podaliri Vulpiani M, et al. Bone Regeneration Induced by Bone Porcine Block with Bone Marrow Stromal Stem Cells in a Minipig Model of Mandibular "Critical Size" Defect. Stem Cells Int. 2017; 2017: 9082869.
9) Gehrke A, Mazon P, Del Fabbro M, Tumedei M, Aramburù J, Perez-Diaz L, et al. Histological and Histomorphometric Analyses of Two Bovine Bone Blocks Implanted in Rabbit Calvaria. Symmetry 2019, 11(5), 641-654. Symmetry. 2019; 11(5): 641-54.
10) Tumedei M, Savadori P, Del Fabbro M. Synthetic Blocks for Bone Regeneration: A Systematic Review and Meta-Analysis. Int J Mol Sci. 2019 Aug 28; 20(17).
11) Buser D, Sennerby L, De Bruyn H. Modern implant dentistry based on osseointegration: 50 years of progress, current trends and open questions. Periodontology 2000. 2017; 73(1): 7-21.
12) Branemark P-I. Osseointegration and its experimental background. J prosthet Dent. 1983; 50: 399-410.
13) Bielemann AM, Marcello-Machado RM, Del Bel Cury AA, Faot F. Systematic review of wound healing bio-

markers in peri-implant crevicular fluid during osseointegration. Arch Oral Biol. 2018 May; 89: 107-28.
14) Morris HF, Ochi S, Winkler S. Implant survival in patients with type 2 diabetes: placement to 36 months. Ann Periodontol. 2000 Dec; 5(1): 157-65.
15) Comuzzi L, Tumedei M, Pontes AE, Piattelli A, Iezzi G. Primary Stability of Dental Implants in Low-Density (10 and 20 pcf) Polyurethane Foam Blocks: Conical vs Cylindrical Implants. Int J Environ Res Public Health. 2020 Apr 11; 17(8).
16) Scarano A, Noumbissi S, Gupta S, Inchingolo F, Stilla P, Lorusso F. Scanning Electron Microscopy Analysis and Energy Dispersion X-ray Microanalysis to Evaluate the Effects of Decontamination Chemicals and Heat Sterilization on Implant Surgical Drills: Zirconia vs. Steel. Applied Sciences. 2019; 9(14): 2837.
17) Comuzzi L, Iezzi G, Piattelli A, Tumedei M. An In Vitro Evaluation, on Polyurethane Foam Sheets, of the Insertion Torque (IT) Values, Pull-Out Torque Values, and Resonance Frequency Analysis (RFA) of NanoShort Dental Implants. Polymers (Basel). 2019 Jun 10; 11(6).
18) Comuzzi L, Tumedei M, Piattelli A, Iezzi G. Short vs. Standard Length Cone Morse Connection Implants: An In Vitro Pilot Study in Low Density Polyurethane Foam. Symmetry. 2019; 11(11): 1349.
19) Scarano A, Piattelli A, Assenza B, Sollazzo V, Lucchese A, Carinci F. Assessment of pain associated with insertion torque of dental implants. A prospective, randomized-controlled study. Int J Immunopathol Pharmacol. 2011 Jun; 24(2 Suppl): 65-9.
20) Maglione M, Bevilacqua L, Dotto F, Costantinides F, Lorusso F, Scarano A. Observational Study on the Preparation of the Implant Site with Piezosurgery vs. Drill: Comparison between the Two Methods in terms of Postoperative Pain, Surgical Times, and Operational Advantages. BioMed research international. 2019;2019.
21) Scarano A, Lorusso F, Noumbissi S. Infrared Thermographic Evaluation of Temperature Modifications Induced during Implant Site Preparation with Steel vs. Zirconia Implant Drill. Journal of Clinical Medicine. 2020; 9(1): 148.
22) Scarano A, Lorusso F, Noumbissi S. Infrared Thermographic Evaluation of Temperature Modifications Induced during Implant Site Preparation with Steel vs. Zirconia Implant Drill. J Clin Med. 2020 Jan 5; 9(1).
23) Alsahhaf A, Al-Aali KA, Alshagroud RS, Alshiddi IF, Alrahlah A, Abduljabbar T, et al. Comparison of yeast species in the subgingival oral biofilm of individuals with type 2 diabetes and peri-implantitis and individuals with peri-implantitis without diabetes. J Periodontol. 2019; 90(12): 1383-9.
24) Monje A, Catena A, Borgnakke WS. Association between diabetes mellitus/hyperglycaemia and peri-implant diseases: Systematic review and meta-analysis. J Clin Periodontol. 2017 Jun; 44(6): 636-48.
25) Pan H, Wu N, Yang T, He W. Association between bone mineral density and type 1 diabetes mellitus: a meta-analysis of cross-sectional studies. Diabetes Metab Res Rev. 2014 Oct; 30(7): 531-42.
26) Scarano A, Di Domizio P, Petrone G, Iezzi G, Piattelli A. Implant periapical lesion: a clinical and histologic case report. J Oral Implantol. 2000; 26(2): 109-13.
27) Noumbissi S, Scarano A, Gupta S. A Literature Review Study on Atomic Ions Dissolution of Titanium and Its Alloys in Implant Dentistry. Materials (Basel). 2019 Jan 24; 12(3).
28) Eskow CC, Oates TW. Dental Implant Survival and Complication Rate over 2 Years for Individuals with Poorly Controlled Type 2 Diabetes Mellitus. Clin Implant Dent Relat Res. 2017 Jun;19(3):423–31.
29) Naujokat H, Kunzendorf B, Wiltfang J. Dental implants and diabetes mellitus-a systematic review. Int J Implant Dent [Internet]. 2016 Feb 11 [cited 2020 May 19]; 2(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5005734/
30) Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract. 2019 Nov; 157: 107843.
31) American Diabetes Association. (2) Classification and diagnosis of diabetes. Diabetes Care. 2015 Jan; 38 Suppl: S8–16.
32) Salvi GE, Carollo-Bittel B, Lang NP. Effects of diabetes mellitus on periodontal and peri-implant conditions: update on associations and risks. J Clin Periodontol. 2008 Sep; 35(8 Suppl): 398-409.
33) Al Zahrani S, Al Mutairi AA. Crestal Bone Loss Around Submerged and Non-Submerged Dental Implants in Individuals with Type-2 Diabetes Mellitus: A 7-Year Prospective Clinical Study. Med Princ Pract. 2019; 28(1): 75-81.
34) Chrcanovic BR, Albrektsson T, Wennerberg A. Diabetes and oral implant failure: a systematic review. J Dent Res. 2014 Sep; 93(9): 859-67.
35) Karaa A, Goldstein A. The spectrum of clinical presentation, diagnosis, and management of mitochondrial forms of diabetes. Pediatr Diabetes. 2015 Feb; 16(1): 1-9.
36. Yu T, Acharya A, Mattheos N, Li S, Ziebolz D, Schmalz G, et al. Molecular mechanisms linking peri-implantitis and type 2 diabetes mellitus revealed by transcriptomic analysis. PeerJ. 2019; 7: e7124.
37) Javed F, Romanos GE. Impact of diabetes mellitus and glycemic control on the osseointegration of dental implants: a systematic literature review. J Periodontol. 2009 Nov; 80(11): 1719-30.
38) Chambrone L, Palma LF. Current status of dental implants survival and peri-implant bone loss in patients with uncontrolled type-2 diabetes mellitus. Curr Opin Endocrinol Diabetes Obes. 2019;26(4): 219-22.
39) Al-Sowygh ZH, Ghani SMA, Sergis K, Vohra F, Akram Z. Peri-implant conditions and levels of advanced glycation end products among patients with different glycemic control. Clin Implant Dent Relat Res. 2018 Jun; 20(3): 345-51.
40) Moraschini V, Barboza ESP, Peixoto GA. The impact of diabetes on dental implant failure: a systematic review and meta-analysis. Int J Oral Maxillofac Surg. 2016 Oct; 45(10): 1237-45.
41) Ormianer Z, Block J, Matalon S, Kohen J. The Effect of Moderately Controlled Type 2 Diabetes on Dental Implant Survival and Peri-implant Bone Loss: A Long-Term Retrospective Study. Int J Oral Maxillofac Implants. 2018 Apr; 33(2): 389-94.
42) Lorusso F, Inchingolo F, Scarano A. Scientific Production in Dentistry: The National Panorama through a Bib-

liometric Study of Italian Academies. BioMed Research International. 2020; 2020.
43) Tetè S, Zizzari VL, De Carlo A, Lorusso F, Di Nicola M, Piattelli A, et al. Characterizing scientific production of Italian Oral Surgery professionals through evaluation of bibliometric indices. Ann Stomatol (Roma). 2014 Jan; 5(1): 23-9.
44) Zizzari VL, De Carlo A, Lorusso F, Tetè S, Piattelli A. Evaluation of scientific production in oral surgery in Italy from 1998 to 2012. Minerva Stomatol. 2014 May; 63(5): 155-65.
45) Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009 Jul 21; 6(7): e1000097.
46) Shahen VA, Gerbaix M, Koeppenkastrop S, Lim SF, McFarlane KE, Nguyen ANL, et al. Multifactorial effects of hyperglycaemia, hyperinsulinemia and inflammation on bone remodelling in type 2 diabetes mellitus. Cytokine Growth Factor Rev. 2020 Apr 17;
47) Yoho RM, Frerichs J, Dodson NB, Greenhagen R, Greenhagan R, Geletta S. A comparison of vitamin D levels in nondiabetic and diabetic patient populations. J Am Podiatr Med Assoc. 2009 Feb; 99(1): 35-41.
48) Inaba M, Nishizawa Y, Mita K, Kumeda Y, Emoto M, Kawagishi T, et al. Poor glycemic control impairs the response of biochemical parameters of bone formation and resorption to exogenous 1,25-dihydroxyvitamin D3 in patients with type 2 diabetes. Osteoporos Int. 1999; 9(6): 525-31.
49) van Lierop AH, Hamdy N a. T, van der Meer RW, Jonker JT, Lamb HJ, Rijzewijk LJ, et al. Distinct effects of pioglitazone and metformin on circulating sclerostin and biochemical markers of bone turnover in men with type 2 diabetes mellitus. Eur J Endocrinol. 2012 Apr; 166(4): 711-6.
50) Gaudio A, Privitera F, Battaglia K, Torrisi V, Sidoti MH, Pulvirenti I, et al. Sclerostin levels associated with inhibition of the Wnt/β-catenin signaling and reduced bone turnover in type 2 diabetes mellitus. J Clin Endocrinol Metab. 2012 Oct; 97(10): 3744-50.
51) Neumann T, Hofbauer LC, Rauner M, Lodes S, Kästner B, Franke S, et al. Clinical and endocrine correlates of circulating sclerostin levels in patients with type 1 diabetes mellitus. Clin Endocrinol (Oxf). 2014 May;80(5):649–55.
52) Gennari L, Merlotti D, Valenti R, Ceccarelli E, Ruvio M, Pietrini MG, et al. Circulating sclerostin levels and bone turnover in type 1 and type 2 diabetes. J Clin Endocrinol Metab. 2012 May; 97(5): 1737-44.
53) Tsentidis C, Gourgiotis D, Kossiva L, Marmarinos A, Doulgeraki A, Karavanaki K. Sclerostin distribution in children and adolescents with type 1 diabetes mellitus and correlation with bone metabolism and bone mineral density. Pediatr Diabetes. 2016; 17(4): 289-99.
54) Faienza MF, Ventura A, Delvecchio M, Fusillo A, Piacente L, Aceto G, et al. High Sclerostin and Dickkopf-1 (DKK-1) Serum Levels in Children and Adolescents With Type 1 Diabetes Mellitus. J Clin Endocrinol Metab. 2017 01; 102(4): 1174-81.
55) Moy PK, Medina D, Shetty V, Aghaloo TL. Dental implant failure rates and associated risk factors. Int J Oral Maxillofac Implants. 2005 Aug; 20(4): 569-77.
56) Alsaadi G, Quirynen M, Komárek A, van Steenberghe D. Impact of local and systemic factors on the incidence of oral implant failures, up to abutment connection. J Clin Periodontol. 2007 Jul; 34(7): 610-7.
57) van Steenberghe D, Jacobs R, Desnyder M, Maffei G, Quirynen M. The relative impact of local and endogenous patient-related factors on implant failure up to the abutment stage. Clin Oral Implants Res. 2002 Dec;13(6):617–22.
58) Héron E, Deloukas P, van Loon AP. The complete exon-intron structure of the 156-kb human gene NFKB1, which encodes the p105 and p50 proteins of transcription factors NF-kappa B and I kappa B-gamma: implications for NF-kappa B-mediated signal transduction. Genomics. 1995 Dec 10; 30(3): 493-505.
59) Candel-Martí M-E, Flichy-Fernández A-J, Alegre-Domingo T, Ata-Ali J, Peñarrocha-Diago MA. Interleukins IL-6, IL-8, IL-10, IL-12 and periimplant disease. An update. Med Oral Patol Oral Cir Bucal. 2011 Jul 1; 16(4): e518-521.
60) Amzel LM, Huang C-H, Mandelker D, Lengauer C, Gabelli SB, Vogelstein B. Structural comparisons of class I phosphoinositide 3-kinases. Nat Rev Cancer. 2008; 8(9): 665-9.
61) Nordberg G, Fowler B, Nordberg M. Handbook on the Toxicology of Metals: Fourth Edition , 1, pp. 1-1385. Handbook on the Toxicology of Metals: Fourth Edition. 2014. 1-1385. p.
62) Bornstein MM, Cionca N, Mombelli A. Systemic conditions and treatments as risks for implant therapy. Int J Oral Maxillofac Implants. 2009 ;24 Suppl: 12-27.
63) Thomas MV, Puleo DA. Infection, inflammation, and bone regeneration: a paradoxical relationship. J Dent Res. 2011 Sep;90(9):1052–61.
64) Heitz-Mayfield LJA. Peri-implant diseases: diagnosis and risk indicators. J Clin Periodontol. 2008 Sep;35(8 Suppl): 292-304.
65) Ferreira SD, Silva GLM, Cortelli JR, Costa JE, Costa FO. Prevalence and risk variables for peri-implant disease in Brazilian subjects. J Clin Periodontol. 2006 Dec; 33(12): 929-35.
66) Lindhe J, Meyle J, Group D of European Workshop on Periodontology. Peri-implant diseases: Consensus Report of the Sixth European Workshop on Periodontology. J Clin Periodontol. 2008 Sep; 35(8 Suppl): 282-5.
67) Rosen, Clem D, Cochran D, Froum S, McAllister, Renvert, et al. Peri-implant mucositis and peri-implantitis: a current understanding of their diagnoses and clinical implications Rosen, P., Clem, D., Cochran, D., Froum, S., McAllister, B., Renvert, S., Wang, H.-L. J Periodontol. 2013 Apr; 84(4): 436-43.
68) Klokkevold PR, Han TJ. How do smoking, diabetes, and periodontitis affect outcomes of implant treatment? Int J Oral Maxillofac Implants. 2007; 22 Suppl:173-202.
69) de Morais JAND, Trindade-Suedam IK, Pepato MT, Marcantonio E, Wenzel A, Scaf G. Effect of diabetes mellitus and insulin therapy on bone density around osseointegrated dental implants: a digital subtraction radiography study in rats. Clin Oral Implants Res. 2009 Aug; 20(8): 796-801.
70) Piattelli A, Sabatino G, Chiarelli F, Verrotti A, Trisi P. [Periodontal disease and insulin-dependent diabetes. Clinical study]. Dent Cadmos. 1990 May 31; 58(9): 72-83.
71) Sam L, Chattipakorn S, Khongkhunthian P. Obesity and

dental implant treatment: a review. Journal of Osseointegration. 2018; 95-102.
72) Cicuttini FM, Baker JR, Spector TD. The association of obesity with osteoarthritis of the hand and knee in women: a twin study. J Rheumatol. 1996; 23(7): 1221-6.

Author Contributions:
Conceptualization, AS and FL.; methodology, AS and FL.; software, FL.; validation, AS FL., MD, BR; formal analysis, FL AS; investigation, AS FL.; data curation, AS FL MD BR.; writing-original draft preparation, AS, FL.; writing-review and editing, AS, FL.; visualization, AS, FL MD, BR.; supervision, AS.;

Corresponding Author:
Prof. Antonio Scarano
Department of Medical, Oral and Biotechnological Sciences, University of Chieti-Pescara
Via dei Vestini 31
66100 Chieti, Italy
Email: ascarano@unich.it
(Italy)