The bad relationship, osteo-decay and diabetes type 2 searching for a link: a literature review

C. Gargiulo Isacco[1,2,3*], A.D. Inchingolo[1*], K.D. Nguyen Cao[1,2,3], G. Malcangi[1], G. Paduanelli[1], V. Pham Hung[2], T. Tran Cong[2], I.R. Bordea[4], A. Scarano[5], A. Laforgia[1], G. Marinelli[1], L. Limongelli[1], F. Inchingolo[1†], F. Lorusso[5†], A.M. Inchingolo[1†] and G. Dipalma[1†]

[1]Department of Interdisciplinary Medicine, University of Medicine Aldo Moro, Bari, Italy; [2]Phan Chau Trinh University of Medicine Hoi An City, Vietnam; [3]Human Stem Cells Research Center of Ho Chi Minh City Vietnam; [4]Department of Oral Rehabilitation, Faculty of Dentistry, Iuliu Haţieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania; [5]Department of Innovative Technologies in Medicine and Dentistry, University of Chieti-Pescara, Chieti, Italy

[*]These authors contributed equally to this work as co-first Authors.
[†]These authors contributed equally to this work as co-last Authors.

The diabetes and osteoporotic metabolic diseases are characterized by a wide prevalence of the population worldwide and correlated to alteration of the bone tissues. Several cofactors could influence the clinical course and the biochemistry of the pathologies such as human microbiome, nutrition characteristics, gut microbiota activity and interactions with vitamin K and D across IGF/GH and TP53 signaling pathways and the glucose/energy as mechanism for bone tissue health. Moreover, also the calories and sugar consumption seem to be correlated to an increased inflammatory state with several consequences for hematopoiesis and host tissues response. The aim of the present literature review was to highlight the role of osteoporotic diseases and diabetes type 2 link for the bone metabolism. The literature cases showed that a correlation between bone-gut-kidney-heart-CNS-Immunity crosstalk seems to be linked with bone metabolism and health regulation. Moreover, also the aging process could represent a valuable co-factor for the sustaining of the metabolic disorders upon a multi-systemic level.

Diabetes complications and osteoporotic fractures are two of the most important causes of morbidity and mortality in elderly patients and share many features including genetic susceptibility, molecular mechanisms, and environmental factors (1). Type 2 diabetes mellitus (DM2) compromises bone microarchitecture by inducing abnormal bone cell function and matrix structure, with increased osteoblast apoptosis, diminished osteoblast differentiation, and enhanced osteoclast-mediated bone resorption (2). The relation between these two metabolic types of disease has to be found within three areas, the micro-molecular compartment of gut microbiota, at the energy regulatory level of intracellular compartment, at the mesenchymal stem cell (MSCs) differentiation apparatus to osteoblasts and, at the neuro-endocrine regulatory compartment of hormones and immune responses (4-6). Both glycemic and bone homeostasis mechanisms share the same regulatory factors and interface with the same signaling pathways. Despite the rapid progress in understanding the role of the different signaling pathways that links the skeleton homeostasis and diabetes insurgence doubts remain. For instance, it

Key words: Diabetes type 1-2; metabolic syndrome; enteric nervous system; central nervous system; mesenchymal stem cells; bone marrow; mTOR; IGF-1-2 PT53; Wnt; Rank-l; receptor activator NF kappa B ligand (NFκB-RANK); osteoblasts; mitochondria; ATP; ROS; telomere/telomerase; ageing

Corresponding Author:
Dr. Felice Lorusso,
Department of Innovative Technologies in Medicine and Dentistry,
University of Chieti-Pescara, Chieti, Italy
e-mail: drlorussofelice@gmail

0393-974X (2020)

is still unclear the signal inputs within the mTOR pathways and the corresponding mechanisms for activating mTORC1 versus mTORC2 and the effective role of PT53, secondly how this defection may compromise the regenerative mechanism which involves the activation of MSCs from BM.

Current outcomes have confirmed the co-expression of multiple growth factors, proteins and hormones including Wnt, IGF1-2, and Bmp that may definitively play a role along the whole axis that links together gut, skeleton, and metabolism. Any disturbance of this mechanism may trigger a cascade that will negatively affect bone homeostasis, bone cell differentiation and bone remodeling process. The types of dysfunction may include changes in intracellular pH balance, the over-expression of ROS, the increase of pro-inflammatory signaling pathways, the accumulation of CO_2 and toxins within intracellular space and in tissue. The side-effects may be also seen to affects the immune-endocrine-metabolic system at the level of central nervous system (CNS) and the enteric nervous system (ENS) of the gut. This small review's aim is to briefly explore the systemic impact of endocrine-metabolic dysfunctions in bone homeostasis decay and the gradual uprising of DM2, elucidating the key role of skeleton system in preserving health and regenerative process.

DISCUSSION

Nutrition, human microbiome and metabolic syndrome

During last few decades, in both Western and Eastern countries it has been experienced an exponential increase of non-communicable diseases, such as allergies, autoimmune disorders, and inflammatory conditions. The incidence of Diabetes for instance has reached an alarming

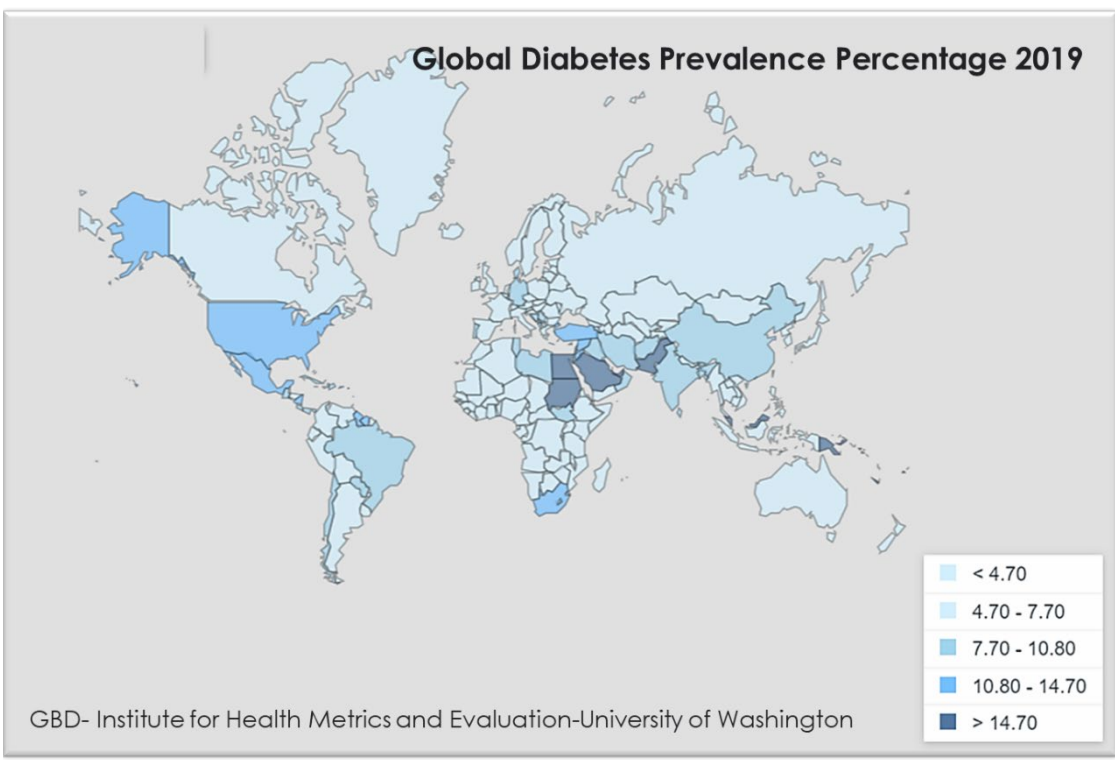

Fig. 1. *The prevalence of diabetes worldwide in the 2019. The data were obtained by the Global Health Data electronic database (GBD Institute for Health Metrics and Evaluation-University of Washington) (3).*

level and has become a major lifestyle metabolic disorder globally, in developing Asian countries it contributes to more than 60% of the world's diabetic population (Fig.1, 2) (7, 8).

Important data, mainly from nutrition science, stressed out the protecting effects of a balanced and uncontaminated diet versus the consequences of the ageing process inducing more regenerative responses. Findings have indicated that ageing and physiological decay are strictly correlated with weakening of the adult stem cell regeneration process as consequence of high industrial processed food intake (9).

Metabolic syndrome (MSy) is a consequence of the modern industrialized fatty/sugar food production that includes severe clinical complications such as dyslipidemia, hypertension, diabetes and dementia that share underlying common pathophysiological mechanisms. Unhealthy fat and toxins buildup predispose individuals to MSy, the long term presence accumulation of adipose tissue may negatively affect the correct functionality of pituitary/hypothalamus system indirectly interfering with the normal relation within organs (10-14)resulting in clinical conditions such as metabolic syndrome, early atherosclerosis, dyslipidemia, hypertension and type 2 diabetes (T2D.

The core momentum has to be searched within the gut system. Simple chain refined carbohydrates and sugars are fermented by specific gut bacteria and are broken down into short-chain fatty acids (SCFAs), primarily acetate, propionate, and butyrate. The importance of SCFAs is based on their role in modulating the use of energy derived from the diet through the interaction G protein-coupled receptor 41-43 (GPR41-43) with special entero-endocrine cells that are in charge of inducing the secretion of peptide YY (PYY) that in turn enables food transit in the intestines. The special commitment of GPR43 is characterized by the activation of the glucagon-like peptide 1 (GLP-1) essential in the constant insulin

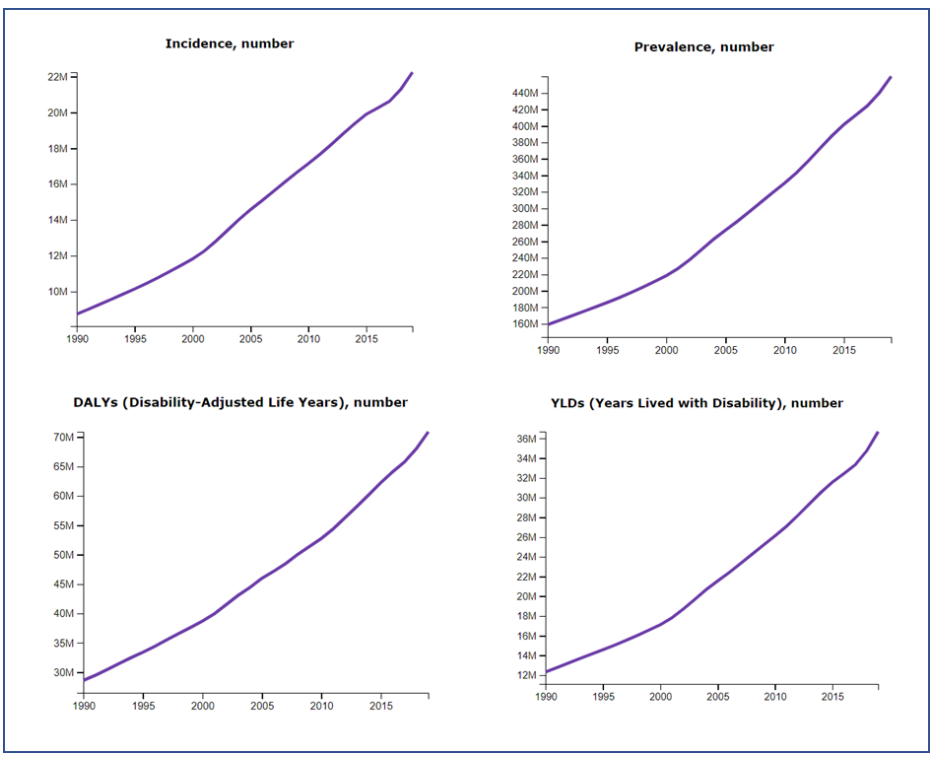

Fig. 2. *The incidence, prevalence, DALYs (disability-adjusted life years) and YLDs (Years Lived with disability) of diabetes worldwide in the 2019. The data were obtained by the Global Health Data electronic database (GBD Institute for Health Metrics and Evaluation-University of Washington) (3).*

sensitivity. The gut microbiota work based on a finely coordination between leptin, insulin hypothalamus hormone axis and, by this way can regulate the fasting-induced adipose factor (Fiaf) expression in the ileum, a key factor in blocking the lipoprotein lipase (LPL) for fat storage in white adipose tissue to prevent excessive fat accumulation. The SCFAs also activate the intestinal gluconeogenesis (IGN mechanism) via the ENS pathway improving the glucose metabolism decisive in the satiety level mechanism (15-20).

Stem cells/osteoblast disrupted differentiation pathway in DM II: the role of dysbiosis

The dysfunction of gut microbiome generates an event known as dysbiosis, a condition characterized by the abnormal balance between all different constituents of the gut micro-flora which predisposes an over accumulation of humus of indigested starches and sugars in the intestinal epithelium (21)dental stem cells from apical papilla (SCAPs. In the medium, long term, this accumulation leads to the intensification of methane, hydrogen, and nitrogen gases with a consequent inhibitory effect on the local compensatory/ regulatory mechanism. The main relevant end-point is seen with the upsurge of both fermenting bacteria and the increase of pH acid level that favor uncontrolled auto-immune responses and the uprising of a systemic chronic inflammatory state (15-19).

Though apparently may seem incongruous, the connection diabetes/bone degeneration should be seen in the gut subverted environment otherwise known as "diabetic stem cell mobilopathy" and "diabetes induced bone marrow micro-angiopathy", conditions which indicate impairments of the stem cell differentiation and mobilization mechanisms (22-26)and their cell surface marker profiles change during the process of mobilization and maturation. Hence, a generally accepted marker combination and a standardized protocol for the quantification of EPCs remain to be established. To determine the EPC subsets that are affected by diabetes, we comprehensively analyzed 32 surface marker combinations of mouse peripheral blood (PB. The reduced availability of circulating stem cells and downregulation of both osteoblast and endothelial progenitor cells (EPCs) caused by hyperglycemia and the oxidative stress together with consistent acidic pH microenvironment are among the several causes accountable for the occurrence of endothelial dysfunction in cardiovascular disease and bone decay in diabetic patients (25, 27-29)and their cell surface marker profiles change during the process of mobilization and maturation. Hence, a generally accepted marker combination and a standardized protocol for the quantification of EPCs remain to be established. To determine the EPC subsets that are affected by diabetes, we comprehensively analyzed 32 surface marker combinations of mouse peripheral blood (PB.

More specific, chronic gut dysbiosis is characterized by local physiological alteration due to uncontrolled increase of different types of bacteria such as the Firmicutes, Staphylococcus, Enterobacteriaceae and E coli, changes that are clinically confirmed in patients diagnosed with gut inflammatory disease like Crohn's disease and ulcerative colitis who also are affected by osteoporosis and osteopenia (30, 31).

Hormones, bones and diabetes

Molecularly, one of the mechanisms involved may be related to deficits incurred in the RANKL (receptor activator NF kappa B ligand NFκB-RANK), osteocalcin (OCN), osteoprotegerin (OPG) and, the immunoreceptor tyrosine-based activation motif (ITAM) system. Noteworthy, the RANKL, OPG and ITAM are members of the TNF super-family and share the same signaling pathway of androgen hormones (32).

The activation in mononuclear cells of NFκB which coordinates the transcription of IL-1, IL-6, IL-8, and other peptides increase important inflammatory responses up-regulating viciously the expression of pro-inflammatory genes such as TNF-α, adhesion molecules, and different chemokines generating a consistent and perturbing inflammatory state typical of metabolic related disorders (33-35).

A further co-related effect linked to these disturbances is the inhibitory effect on the hypothalamus/pituitary/adrenal axis with a further and progressive decay of testosterone, estrogen and progesterone and the augmentation of pro-inflammatory factors such as TNFα. However, deficits in testosterone levels are common in men with Type

2 diabetes. Such men are characterized by normal gonadotropin responses to gonadotropin releasing hormone stimulation (24-26).

It is interesting to note how the frequency of androgen deficiency in male patients with MSy and DM2 has been seen more than a simple coincidence, the outcomes showed how this association is in real much higher than that in the normal population. Data found that the prevalence low testosterone levels in DM2 reached almost 40% either Europe or China (36-38).

Granim and colleagues recently showed that following testosterone treatment it was noted a substantial increase in serum OCN concentrations, they endpoint showed the change from baseline in OCN at week 23 of the study group significantly higher than the placebo group [mean change (95% CI), 3.52 [0.45, 6.59], P = 0.008] (37).

Of note in this situation the OPG is concomitantly down regulated that in turn induces an uncontrolled osteoclast hyper-activity. The OPG which main activity is the modulatory activity of the osteoclastogenesis via RANK pathway is expressed primarily by BM stromal MSCs whilst can be activated in B lymphocytes, follicular DCs, and could be regulated positively by TGF-β, IL-1, TNF, estrogen, Wnt ligands and negatively regulated by prostaglandin E2 (PGE2) and glucocorticoids. At this point it is essential to remark that the progressive decrease of testosterone, estrogen and progesterone witnessed in diabetic individuals reveals a complex situation. A scenario characterized by a compromised regenerative process of MSCs within the BM niches concomitant to an elevated systemic inflammatory state on one hand and, a skeleton system steady decay related to the decline of both OPG and OCN functionality, on the other hand (39-41).

Gut microbiota, calcium absorption and the role of vitamin K and D

Diabetes type 2, vascular calcification and osteoporosis involve the same degenerative mechanisms all related to gut dysbiosis in which the synthesis of important molecules such as the vitamin K provokes deep homeostatic deteriorations. The vitamin K deficiency triggers the so called "calcium

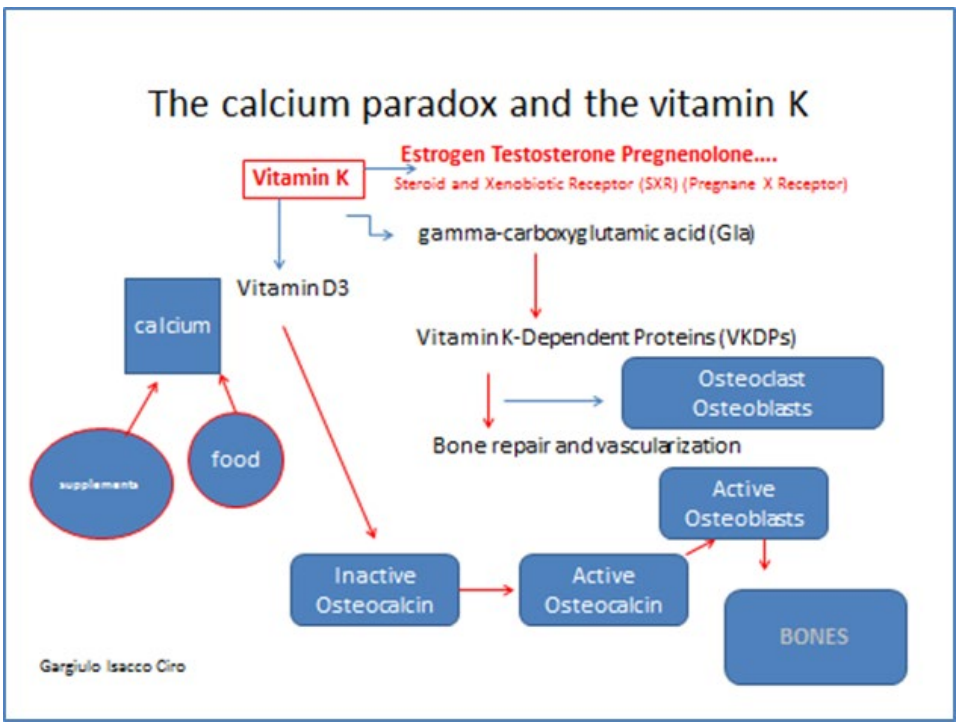

Fig 3. *The important role of Vitamin K in formation of bone and osteoblasts activation and regulating bone homeostasis (Gargiulo Isacco Ciro).*

paradox", that is contradistinguished by the lack of calcium in the bone and its ectopic deposit in different location other the skeleton such as, the vessel walls, bone surfaces (osteophytes) and joints (42-49).

The role of vitamin K in bone formation and bone homeostasis has been for long time neglected, Vitamin K participates as coenzyme for the gamma-Glutamyl CarboXylase (GGCX) enzyme formation inside the endoplasmic reticulum that catalyzes the carboxylation of glutamic acid residues (Glu), which in turns once converted into gamma-carboxyglutamic acid (Gla) enhances the activity of Vitamin K-Dependent Proteins (VKDPs). The importance of VKDPs is their involvement in the vascular and bone tissue repair mainly thanks to the activity of the bone Gla protein and osteocalcin (50,51).

Of note, the Warfarin anti-coagulant use in patients with cardio vascular diseases (CVD) acts as a Vitamin K antagonist in preventing vitamin K activity by inhibiting two vitamin K correlate enzymes, the epoxide reductase (VKOR) and vitamin K quinone reductase; the long term usage of Warfarin showed evident decay of bone tissue and of note, the VKOR subunit 1(VKORC1) has been also used as a marker for bone degenerative condition (52-55).

The strategic function of VKORC1 as main oxidoreductase enzyme is to allow the absorption of vitamin K quinone by dietary uptake reducing it into the hydroquinone (KH2) form, allowing the entry of vitamin K into the whole vitamin K cycle (55,56). The following steps lead to oxidation of vitamin K hydroquinone to vitamin K 2,3-epoxide (K>O) mechanism that takes

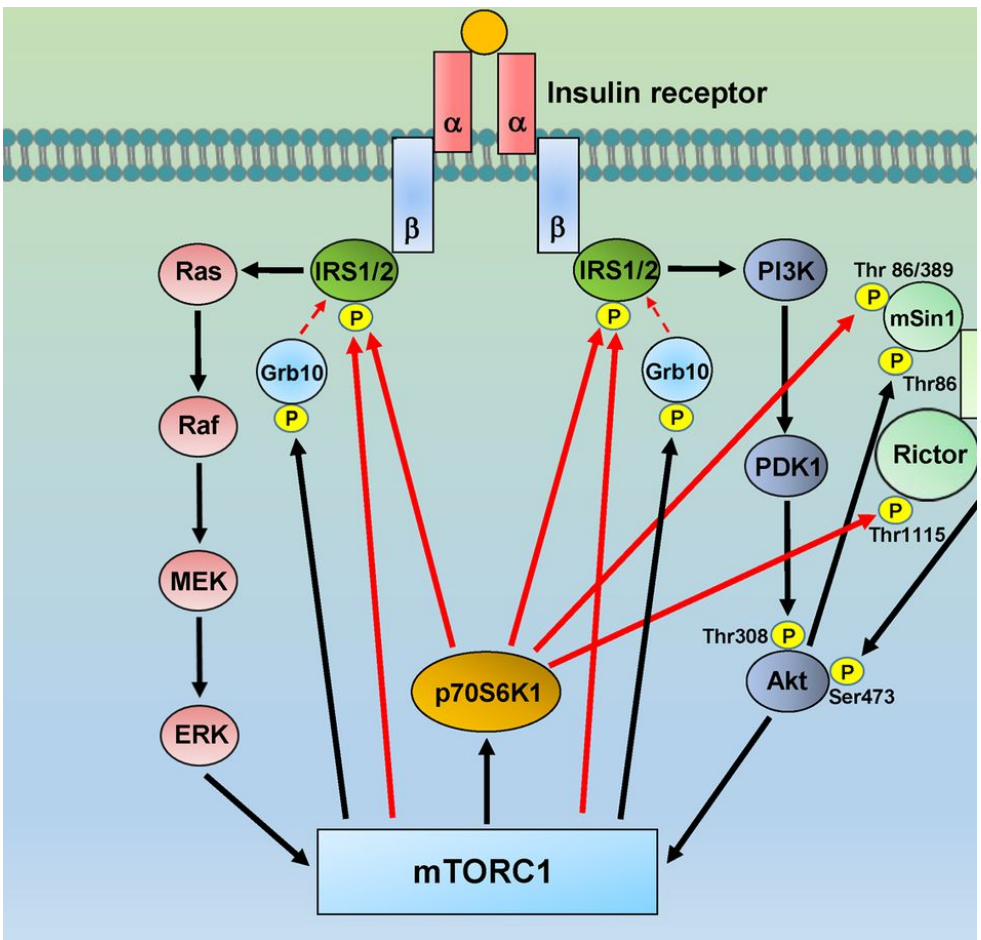

Fig. 4. *The inhibition of IRS under hyper-activation of mTORC1 due to high energy diet such as sugars and refined carbs. The p70S6K plays a pivotal role in inhibiting the IRS that loses its capability of glucose transporters transferring to the cell surface (69).*

place in the post-translational activation of vitamin K-dependent (VKD) phase where are involved proteins in charge of the enzymatic conversion of Glu residues into γ-carboxyglutamate (Gla) residues. The VKORC1 is in charge conclude the cycle by reducing the K>O to K and KH2, to ensure the efficient reuptake of vitamin to lead the necessary following sequences of γ-glutamyl carboxylation (57,58).

Vitamin K may act as ligand of the nuclear receptor for Steroid and Xenobiotic Receptor (SXR) (Pregnane X Receptor, PXR, murine homolog). Kato and colleagues showed that SXRs/PXRs are expressed in osteoblasts and it is activated by vitamin K that in turns up-regulate gene expression such as tsukushi (Tsk), matrilin-2 (Matn2) and CD14 involved in bone morphogenetic and formation (Fig. 3).

The Tsk gene was showed to be important in collagen-accumulating mechanism, the Matn2 is involved in formation of extracellular matrix like collagen, whereas CD14 controls both osteoblast and osteoclast producing mode through B lymphocyte differentiation mechanism, indicating the SXR/PXR-vitamin K mechanism as key regulator of bone homeostasis (56,59,60).

In addition, vitamin K, and specifically K2 in its form of menaquinone 4 and 7 (MK 4-7) were confirmed to inhibit osteoclastic bone resorption, by suppression of RANKL expression (61-67).

The pathway of cell energy consumption, the metabolic role of mTORC1 in insulin resistance

he bone system in mammalian plays a crucial role regulating the whole homeostasis of the body and maintains the pH alkaline/acid of organs, tissues and cells. As mentioned above, in diabetic individuals the bone regenerative mechanism and homeostasis is generally compromised following a chronic accumulation of toxic oxidative derivatives within the intracellular compartment such as the advance glycation end-products [AGEs] that contribute to bone fragility and tissue deterioration. This activity is mainly based on two molecules, the mTORC1 and 2 (mammalian target of rapamycine complex 1 and 2) which are protein complex in charge of osteoblast growth and proliferation and act as cell sensors playing an active part in the control for the cellular energy mechanism. The mTorc1 has been specifically linked with insurgence of both DM1 and DM2 due to the blockage of the insulin receptor substrate (IRS), the high carbs-sugar prolonged diet interferes to the IRS mechanism through the activity of class 1 P13-kinases (p70S6K) crucial for pancreatic β-cells insulin regulation. The high presence of p70S6K inhibits IRS to transfer the glucose transporters on to cells surface let glucose molecules free within systemic circulation; in response to this event the brain/liver/adipose axis force the lipoprotein lipases to decrease and triggering the triglycerides increase (67-86) (Fig 4).

The mTORC1-2 is the key in regulating multiple aspects of bone and cartilage development with mineral addition via specific inhibition exerted on MSCs differentiation mechanism. Either hyper-expression or deletion of mTORC1 via diet mice showed a reduced size of limb bud cells and impaired chondrogenesis from the MSC progenitors (85,86). Evidence is quite clear in showing the involvement of mTORC1-2 within a wider mechanism constituted by a complexity of hormones, growth factors, proteins and immune signaling pathways. The crosstalk takes place at several level and within different modalities, the relation of androgen-receptor and mTOR is mediated by testosterone availability; the IGF-1activates mTORC1-2 signaling to stimulate osteoblast differentiation of bone marrow MSCs, mTORC1 systematically mediates the Wnt osteogenic activity through the activity on glutamin catabolism and IRS 1 and 2 which sequentially promote the expression of protein anabolism gene essential in MSCs differentiation to osteoblasts (Fig. 5-6). Of note the bone morphogentic protein 2 (Bmp2) a protein extremely important in bone formation is partly activated in mTORC1-dependent manner, whereas significant is the involvement of the mTORC2 in bone formation by promoting osteoclastogenesis that takes place by modulating the expression of Rankl (87-99).

Additionally, the mTOR's crosstalk with hormones like the GLP 1-2 also play a crucial position. The GLP 1-2 belongs to the incretin hormone axis released in response to food intake by the L cells through the proglucagon processing in the upper part of intestines (93). Food intake, peptide and CNS involvement through vagal nerve innervation control the GLP-

1 secretion. The intracellular signaling pathway by which all this process takes place and is synchronized still remaining unclear, however we may suppose that L cells may respond in coordination with GLP-1 through mTOR and the presence of the complex net of different hormones like leptin, ghrelin, insulin, androgen hormones and estrogen. In fact, gastric mTOR changes affect negatively the expression and secretion of ghrelin and nesfatin-1/nucleobindin 2 the latter well known as cancer cell migration factors, compromising glucose homeostasis and food intake (93, 100-102).

The IGF/GH and TP53 signaling pathways converge upon the glucose/energy mechanism, a possible key to understand bone health and longevity?

Those invertebrate species that has maintained insulin and insulin-like growth factor (IGF) signaling (IIS) pathway during their evolutionary process manifest a better control of their longevity. However, mammals have a more complicated system that is different one to another that makes even more difficult to correctly understand the mechanism. One of the issues is mainly related to the different biology of mammals and humans which show the insulin, IGF-1 and IGF-2 in different tissues and molecular signaling pathways. Mutated mice for instance like the FIRKO mice, in which the insulin receptor was ablated in fat tissue, showed to live longer. FIRKO mice reduced fat mass and lessened age were concomitant factors related to loss of insulin sensitivity. It should be noted that the expenditure/need of calories and energy supply in rodents and small mammals with fast metabolic rate is extremely high, traits that are extremely different from those in humans (104-110).

In humans, any deficiencies in the insulin signaling pathway lead to insulin resistance and diabetes (111, 112). However, in the Laron syndrome where there are specific defects in the growth hormone-GH/IGF-1 signaling mechanism associated with high risk of cardiovascular disease and obesity, the patients do not develop DM2, condition which seem to have a sort of protection against cancer and show quite

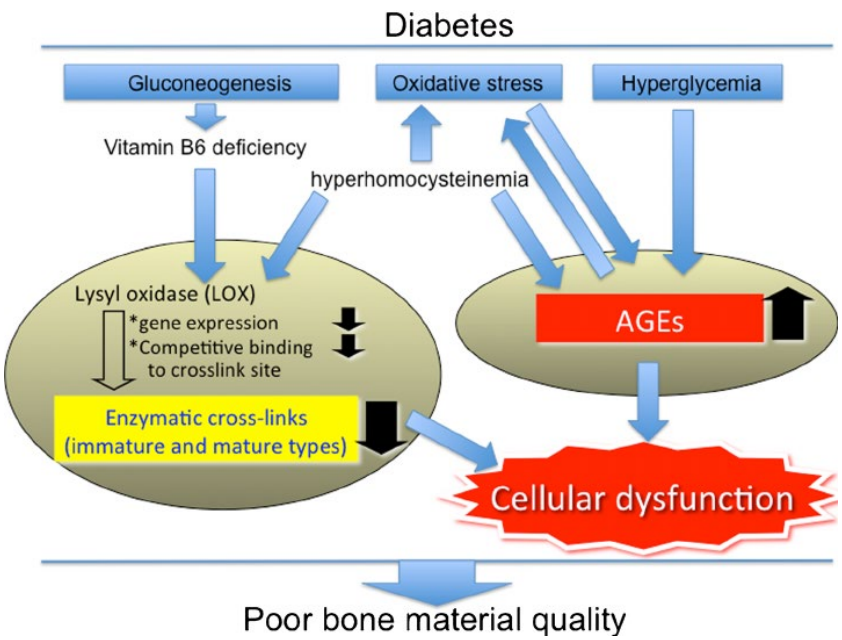

Fig. 5. *The diabetes effects on bone. The glucose and insulin metabolism indirectly alter skeletal muscle signaling, which in turns induce accumulation of AGEs subverting the collagen cross-linking with the impairment on bone remodeling. The glucose/insulin metabolic impairment to the bone is also weakened as the microenvironment signaling pathways are engulfed or mismatching. The changes in bone microenvironment directly impact on MSCs differentiation path to osteoblast resulting in decreased bone formation with higher bone resorption rate with an increased risk of fractures (103).*

a significant longevity (113, 114). Intriguingly, the presence of single nucleotide polymorphism (SNP) was detected in the IIS genes and this was a common pattern of longevity across diverse cohorts. In a group of centenarians in Italy it was seen a common pattern contradistinguished by a low level of IGF-1 in plasma and linked with a specific genotype combination at IGF-IR and PI3KCB gene level (14, 114-116). The most interesting findings come from Dato et al, the team was able to detect repair mechanism shared by specific genes, the TP53-DNA repair pathway/ TXNRD1-pro-antioxidant pathway and TP53-DNA repair pathway/ERCC2-DNA repair pathway (92, 117). The TP53 is a very well-known protein that plays a key role in DNA damage response safeguarding tissues, organs in a conservative/regenerative mode by keeping stem cells pool in stand-by position whilst exerting a powerful anticancer in mediating the DNA repair through the pro-antioxidant pathway or by inducing apoptosis (117).

The interesting fact is that mTOR, TP53, IGF1-2, GLP-1, testosterone, estrogen, progesterone all seems to share some sort of mitochondrial relation. Whereas any impairments on this relation definitely contribute to insulin metabolic dysfunction that also may suggest a clear low expression of specific genes involved in mitochondrial ATP regulation it definitely confirms the strict association between DM2 and healthy bone homeostasis. In fact, mitochondrion serves as energetic control unit of many catabolic and anabolic pathways essential in cell maintenance, activity, proliferation and signal transduction through ROS generation (119-123).

Mitochondria due to their deep involvement into the energy-metabolic activity like ATP production consume the highest amount of cellular oxygen and, of this a consistent part is used for the production of ROS as a by-product of oxidative phosphorylation. In humans and in mammals in general, low calorie consumption showed to reduce the energy outflow with a sensitive saving of oxidative stress and less ROS which in turns improves body energy efficiency use and muscle mitochondrial function (122-126) (Fig. 6).

Telomere/telomerase, energy consumption, inflammation and immune responses towards infectious diseases like COVID-19, HVB and HIV

Saeed and colleagues were able to confirm that telomerase over-expression enhanced BM-MSC differentiation to osteoblasts either in vitro or in

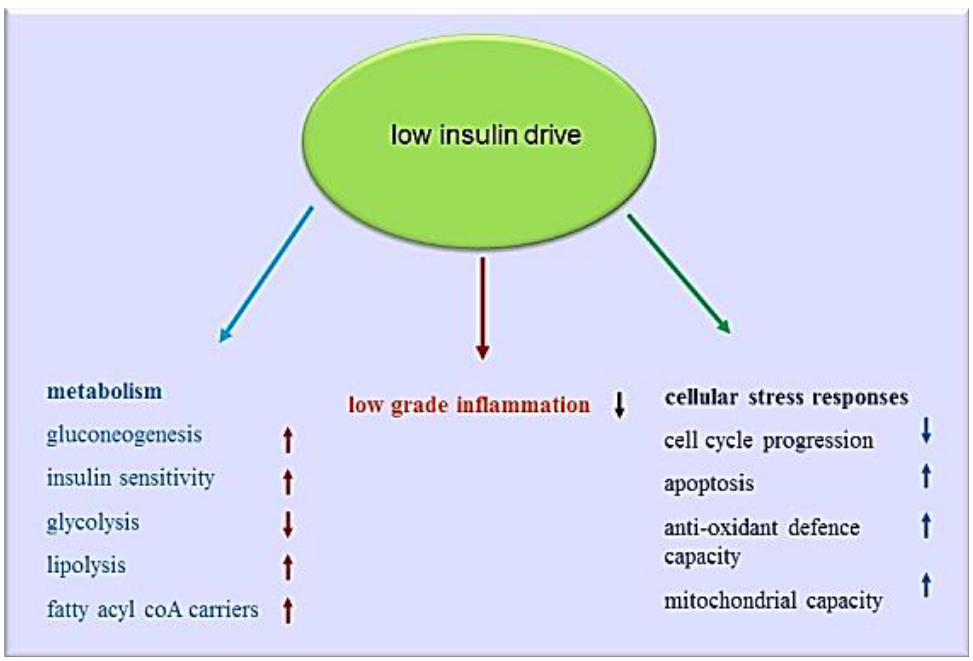

Fig. 6. *A low insulin drive may be associated with metabolic rate, low grade inflammation and cellular stress responses (118).*

vivo. However, telomere and telomerase activity are very susceptible to inflammatory process typical of metabolic disorder due to fat accumulation and insulin resistance seen in DM 1 and 2, CVD and Kidney disorders. The telomere and telomerase are therefore highly sensitive to chronic hyperglycemia and nutritional overload (126-128).

Different are the pro-inflammatory mediators that play a ground role in this condition, for instance the transcription factor NF-κB that is strictly connected with pattern recognition receptor (PRR) signaling and inflammation and patients with DM2 showed a high level of NF-κB, that in turns was identified as key player in the telomere complex (128, 129).

This abnormal condition is a constitutive part of reaction loop contradistinguished by high level of oxidative stress, an over-expression of the protein kinase C pathway (which negatively impact on mitochondria) and, a high ROS expression that keep constantly active pro-inflammatory cytokines. The close relation of DM and telomere shortness, the high presence of inflammatory agents, the subversion of mitochondria activity and the high expression of ROS are intricate portions of a unique interrelated signaling mechanism that eventually led to the inhibition of the regenerative capacity within the BM, in which the MSCs are completely blocked to differentiate to osteoblasts (127-129).

Therefore, shorter telomeres could be seen as indicators of serious degenerative patterns contradistinguished by faster cell senescence and tissue decay, but what about long telomeres? Could the long length telomeres indicate an ongoing disease as well? For instance, increased level of IL-6 and TNF-α which are usually correlated with high levels of CRP have seen reliable forecaster in severe and dangerous inflammatory and age-related disorders they also intensify telomerase activity through the NF-κB, STAT1, and STAT2 activation (130-132). The telomere length may be suggestive of something highly fluctuating contingent to current health status of the patient, in which telomere length maintenance mechanism and the immune system reciprocally affect via telomerase constant adjustments (130, 133-135). Furthermore, carcinogenic-malignant changing cells like melanoma may show high telomerase activity (hTERT) that amplifies telomeric DNA repeats, allowing the cells to escape from apoptosis. The authors suggested it may occur during the very first stage of cancer development in which carcinogenic mutation take place in precursor somatic cells with long telomeres, cells that are constantly target of pro-inflammatory cytokines and NF-kB. In addition, long telomeres provide affected neo-cancerous cells enough replicative potential to avoid any-checkpoint that may inhibit the re-activation of telomerase (136) [111]. It follows that telomere length is not always linked to cell senescence and telomerase activity, telomeres steady shorten during the lifetime but the length is also subject to persistent fluctuations of reductions and repairs, suggestive of an individual's present condition during daily life.

These observations provide support for the hypothesis of a potential metabolic effect of many diseases that are of great threat nowadays, such as COVID-19, HIV or HBV, far beyond the well-recognized stress response associated with severe illness. However, whether the alterations of glucose metabolism and immune responses that may occur with a sudden onset in severe COVID-19 for instance may persist or remit when the infection resolves is unclear. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), this virus is able to bind to angiotensin-converting enzyme 2 (ACE2) receptors, which are expressed in different metabolic organs and tissues, including pancreatic beta cells, adipose tissue, the small intestine, bone and the kidneys. It follows that is plausible that SARS-CoV-2 may trigger multiple alterations in glucose metabolism that could complicate the pathophysiology of preexisting metabolic diseases or lead to new degenerative mechanisms in multiple sites brain, lungs, heart, vessels and bones.

How frequent is the phenomenon of new-onset diabetes, osteo-decay and immunity unbalance it may refer to definitive telomere length reduction or uncontrolled telomerase? Do these patients remain at higher risk for any other type of infection and metabolic disorders? In patients with preexisting metabolic comorbidities such as hypertension, CVD and DM, do Covid-19, HBV or HIV change the underlying pathophysiology and the natural history

of the disease? We need to answer these questions in order to assess wider clinical picture to better understand and monitoring the affected patients (135-141)the derepressed expression of the catalytic subunit of telomerase, human telomerase reverse transcriptase (hTERT.

Conclusion

The biological and molecular scheme that links together subverted immune responses, osteoblast decay and metabolic disorders must be investigated through the vigil eyes of the Regenerative Medicine. The regenerative methodology well explains the entire loop of domino effects that links together troubled gut metabolism, immune/inflammatory responses, mitochondria instability, the deactivated bone marrow MSCs/SCs differentiation mechanism and telomere shortening. In this perspective the initial issues seem to arise from metabolic/catabolic cellular mitochondrial disturbances, the center that regulates the whole energy functions vital to cells, tissues and organs. It follows that any clinical and therapeutic strategy requires a wider and deeper diagnostic evaluation on past and present condition of the patient. Patients with elusive metabolic/immune disorders such as the DM2, CVD and Kidney failure all manifest impairment in regenerative stem cell pathway and more specifically in MSCs differentiation process towards osteoblast phenotype.

Thus, it can be firmly listed that senescence that has not be confused with biological clock ageing, is the final phase long interconnected molecular processes. Despite intensive research over the last two decades and a deeper understanding of the features of immune/metabolic ageing, the whole bunch of molecular mediators that are involved in this chain of events and the extent to which they interact still need a clearer definition. In addition, though the association of telomere length with cellular senescence and decay has been widely researched, the precise relationship between telomere/telomerase activity and the entire sequences of signaling pathways involved in cells and tissue homeostasis still a matter of big debate. A better definition of this crosstalk will be essential to understanding the influence of sugar and calorie overload and the inflammatory reaction on human hematopoiesis and cell/tissue regeneration. The recently identified ability of a hypocaloric diet on stem cells regeneration mechanism to control mitochondria consumption of extra-energy and ROS overload may lead to significant progress in developing strategies of treating degenerative immune/metabolic senescence in a wide range of human diseases like DM and bone decay. Together, these outcomes emphasize the importance of detecting earlier inflammatory responses that could take place in the gut microbiome which led to dysbiosis as a major driver of immune deterioration and senescence advancement as optimal condition for pathogen up rising. These outcomes have also clearly confirmed the presence of a bone-gut-kidney-heart-CNS-Immunity crosstalk, suggesting that the ageing process is a multi-factorial mechanism in which each single component regulates whilst is being regulated.

REFERENCES

1. McMahon MM, Bistrian BR. Host defenses and susceptibility to infection in patients with diabetes mellitus. Infect Dis Clin North Am 1995; 9(1):1-9.
2. Lorusso F, Postiglione F, Delvecchio M, Rapone B, Scarano A. The impact of diabetes in implant oral rehabilitations: a bibliometric study and literature review. Acta Medica 2020; 36:3333.
3. GBD Results Tool | GHDx. Accessed January 20, 2021. http://ghdx.healthdata.org/gbd-results-tool
4. Ballini A, Dipalma G, Isacco CG, et al. Oral microbiota and immune system crosstalk: a translational research. Biology 2020; 9(6):131.
5. Inchingolo F, Martelli FS, Gargiulo Isacco C, et al. Chronic periodontitis and immunity, towards the implementation of a personalized medicine: a translational research on gene Single Nucleotide Polymorphisms (SNPs) linked to chronic oral dysbiosis in 96 Caucasian patients. Biomedicines 2020; 8(5):115.
6. Ballini A, Cantore S, Scacco S, et al. A comparative study on different stemness gene expression between dental pulp stem cells vs. dental bud stem cells. Eur Rev Med Pharmacol Sci 2019; 23(4):1626-1633. doi:10.26355/eurrev_201902_17122

7. Ramachandran A. Trends in prevalence of diabetes in Asian countries. World J Diabetes 2012; 3(6):110.
8. Wu Y, Ding Y, Tanaka Y, Zhang W. Risk factors contributing to type 2 diabetes and recent advances in the treatment and prevention. Int J Med Sci 2014; 11(11):1185-1200.
9. Ahmed ASI, Sheng MH, Wasnik S, Baylink DJ, Lau KHW. Effect of aging on stem cells. World J Exp Med 2017; 7(1):1.
10. Camihort G, Gómez Dumm C, Luna G, et al. Relationship between pituitary and adipose tissue after hypothalamic denervation in the female rat. Cells Tissues Organs 2005; 179(4):192-201.
11. Halpern-Silveira D, Susin LRO, Borges LR, Paiva SI, Assunção MCF, Gonzalez MC. Body weight and fat-free mass changes in a cohort of patients receiving chemotherapy. Support Care Cancer 2010; 18(5):617-25.
12. Halpern A, Mancini MC, Magalhães MEC, et al. Metabolic syndrome, dyslipidemia, hypertension and type 2 diabetes in youth: from diagnosis to treatment. Diabetol Metab Syndr 2010; 2:55.
13. Dohan Ehrenfest DM, Del Corso M, Inchingolo F, Sammartino G, Charrier JB. Platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) in human cell cultures: growth factor release and contradictory results. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010; 110(4):418-22.
14. Dohan Ehrenfest DM, Del Corso M, Inchingolo F, Charrier JB. Selecting a relevant in vitro cell model for testing and comparing the effects of a Choukroun's platelet-rich fibrin (PRF) membrane and a platelet-rich plasma (PRP) gel: tricks and traps. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010; 110(4):409-413.
15. Neergaard JS, Dragsbæk K, Christiansen C, et al. Metabolic syndrome, insulin resistance, and cognitive dysfunction: does your metabolic profile affect your brain? Diabetes 2017; 66(7):1957-1963.
16. Moreno-Indias I, Cardona F, Tinahones FJ, Queipo-Ortuño MI. Impact of the gut microbiota on the development of obesity and type 2 diabetes mellitus. Front Microbiol 2014; 5:190.
17. Parekh PJ, Balart LA, Johnson DA. The influence of the gut microbiome on obesity, metabolic syndrome and gastrointestinal disease. Clin Transl Gastroenterol 2015; 6(6):e91.
18. Hur KY, Lee M-S. Gut microbiota and metabolic disorders. Diabetes Metab J 2015; 39(3):198.
19. Guarner V, Rubio-Ruiz ME. Low-grade systemic inflammation connects aging, metabolic syndrome and cardiovascular disease. Interdiscip Top Gerontol 2015; 40:99-106.
20. Scarano A, Lorusso F, Di Cerbo A, Lucchina AG, Carinci F. Eradication of hairy mouth after oncological resection of the tongue and floor mouth using a diode laser 808 nm. Postoperative pain assessment using thermal infrared imaging. Lasers Surg Med 2019; 51(6):516-21.
21. Cantore S, Ballini A, De Vito D, et al. Characterization of human apical papilla-derived stem cells. J Biol Regul Homeost Agents 2017; 31(4):901-10.
22. Gargiulo C, Pham V, Huynh T, et al. Novel therapeutic strategy in the treatment of diabetes type 2, the use of autologous peripheral blood stem cells in 15 patients: Is there any relation with the Incretin-GLP-1/GIP axis? Br J Med Med Res 2017; 20(7):1-16.
23. DiPersio JF. Diabetic stem-cell "mobilopathy." N Engl J Med 2011; 365(26):2536-38.
24. Seewoodhary J, Evans PJ. Diabetes and stem cells: endogenous effects and reparative mechanisms. Br J Diabetes Vasc Dis 2013; 13(5-6):224-28.
25. Saito H, Yamamoto Y, Yamamoto H. Diabetes alters subsets of endothelial progenitor cells that reside in blood, bone marrow, and spleen. Am J Physiol Cell Physiol 2012; 302(6):C892-C901.
26. Scarano A, de Oliveira PS, Traini T, Lorusso F. Sinus membrane elevation with heterologous cortical lamina: A randomized study of a new surgical technique for maxillary sinus floor augmentation without bone graft. Materials (Basel) 2018; 11(8):1457.
27. van der Flier LG, Clevers H. Stem cells, self-renewal, and differentiation in the intestinal epithelium. Annu Rev Physiol 2009; 71:241-60.
28. Jarajapu YPR, Grant MB. The promise of cell-based therapies for diabetic complications: challenges and solutions. Circ Res 2010; 106(5):854-69.
29. Tonelli M, Muntner P, Lloyd A, et al. Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. Lancet 2012; 380(9844):807-14.

30. Festi D, Schiumerini R, Eusebi LH, Marasco G, Taddia M, Colecchia A. Gut microbiota and metabolic syndrome. World J Gastroenterol 2014; 20(43):16079.
31. Yin F, Banerjee R, Thomas B, et al. Exaggerated inflammation, impaired host defense, and neuropathology in progranulin-deficient mice. J Exp Med 2010; 207(1):117-28.
32. Boyce BF, Xing L. The RANKL/RANK/OPG pathway. Curr Osteoporos Rep 2007; 5(3):98-104.
33. Park JH, Lee NK, Lee SY. Current understanding of RANK signaling in osteoclast differentiation and maturation. Mol Cells 2017; 40(10):706-713.
34. Arango Duque G, Descoteaux A. Macrophage cytokines: involvement in immunity and infectious diseases. Front Immunol 2014; 5:491.
35. Gianatti EJ, Grossmann M. Testosterone deficiency in men with Type 2 diabetes: pathophysiology and treatment. Diabet Med 2020; 37(2):174-186.
36. Walsh MC, Choi Y. Biology of the RANKL-RANK-OPG system in immunity, bone, and beyond. Front Immunol 2014; 5:511.
37. Ghanim H, Dhindsa S, Green K, et al. Increase in osteocalcin following testosterone therapy in men with type 2 diabetes and subnormal free testosterone. J Endocr Soc 2019; 3(8):1617-30.
38. Li S, Zhao Y, Yang Y, et al. Metabolic Effects of testosterone replacement therapy in patients with type 2 diabetes mellitus or metabolic syndrome: a meta-analysis. Int J Endocrinol 2020; 2020: 4732021.
39. Galibert L, Tometsko ME, Anderson DM, Cosman D, Dougall WC. The involvement of multiple tumor necrosis factor receptor (TNFR)-associated factors in the signaling mechanisms of receptor activator of NF-κB, a member of the TNFR superfamily. J Biol Chem 1998; 273(51):34120-27.
40. Collins KH, Paul HA, Reimer RA, Seerattan RA, Hart DA, Herzog W. Relationship between inflammation, the gut microbiota, and metabolic osteoarthritis development: studies in a rat model. Osteoarthritis Cartilage 2015; 23(11):1989-98.
41. Cox LM, Yamanishi S, Sohn J, et al. Altering the intestinal microbiota during a critical developmental window has lasting metabolic consequences. Cell 2014; 158(4):705-721.
42. Flore R, Ponziani FR, Di Rienzo TA, et al. Something more to say about calcium homeostasis: the role of vitamin K2 in vascular calcification and osteoporosis. Eur Rev Med Pharmacol Sci 2013; 17(18):2433-40.
43. Walsh MC, Kim N, Kadono Y, et al. Osteoimmunology: interplay between the immune system and bone metabolism. Annu Rev Immunol 2006; 24(1):33-63.
44. Scarano A, Lorusso F, Ravera L, Mortellaro C, Piattelli A. Bone regeneration in iliac crestal defects: an experimental study on sheep. BioMed Res Int 2016; 2016:4086870.
45. Scarano A, Carinci F, Lorusso F, et al. Ultrasonic vs drill implant site preparation: post-operative pain measurement through VAS, swelling and crestal bone remodeling: a randomized clinical study. Materials (Basel) 2018; 11(12):2516.
46. Scarano A, Lorusso F, Arcangelo M, D'Arcangelo C, Celletti R, de Oliveira PS. Lateral sinus floor elevation performed with trapezoidal and modified triangular flap designs: a randomized pilot study of post-operative pain using thermal infrared imaging. Int J Environ Res Public Health 2018; 15(6):1277.
47. Scarano A, Crincoli V, Di Benedetto A, 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.
48. Scarano A, Valbonetti L, Marchetti M, Lorusso F, Ceccarelli M. Soft tissue augmentation of the face with autologous platelet-derived growth factors and tricalcium phosphate. Microtomography evaluation of mice. J Craniofac Surg 2016; 27(5):1212-14.
49. Scarano A, Inchingolo F, Murmura G, Traini T, Piattelli A, Lorusso F. Three-dimensional architecture and mechanical properties of bovine bone mixed with autologous platelet liquid, blood, or physiological water: an in vitro study. Int J Mol Sci 2018; 19(4):1230.
50. Iwamoto J, Takeda T, Sato Y. Interventions to prevent bone loss in astronauts during space flight. Keio J Med 2005; 54(2):55-59.
51. Shearer MJ, Newman P. Recent trends in the metabolism and cell biology of vitamin K with special reference to vitamin K cycling and MK-4 biosynthesis. J Lipid Res 2014; 55(3):345-62.
52. Fusaro M, Mereu MC, Aghi A, Iervasi G, Gallieni

M. Vitamin K and bone. Clin Cases Miner Bone Metab 2017; 14(2):200-6.
53. Danziger J. Vitamin K-dependent proteins, warfarin, and vascular calcification. Clin J Am Soc Nephrol 2008; 3(5):1504-10.
54. Price PA, Faus SA, Williamson MK. Warfarin causes rapid calcification of the elastic lamellae in rat arteries and heart valves. Arterioscler Thromb Vasc Biol 1998; 18(9):1400-7.
55. Violi F, Lip GY, Pignatelli P, Pastori D. Interaction between dietary vitamin K intake and anticoagulation by vitamin K antagonists: Is it really true? A systemic review. Medicine (Baltimore) 2016; 95(10):e2895.
56. Gröber U, Reichrath J, Holick M, Kisters K. Vitamin K: an old vitamin in a new perspective. Dermatoendocrinol 2014; 6(1):e968490.
57. Oldenburg J, Bevans CG, Müller CR, Watzka M. Vitamin K epoxide reductase complex subunit 1 (VKORC1): the key protein of the vitamin k cycle. Antioxid Redox Signal 2006; 8(3-4):347-353.
58. Shearer MJ, Newman P. Recent trends in the metabolism and cell biology of vitamin K with special reference to vitamin K cycling and MK-4 biosynthesis. J Lipid Res 2014; 55(3):345-62.
59. Willems BAG, Vermeer C, Reutelingsperger CPM, Schurgers LJ. The realm of vitamin K dependent proteins: Shifting from coagulation toward calcification. Mol Nutr Food Res 2014; 58(8):1620-35.
60. Azuma K, Casey SC, Ito M, et al. Pregnane X receptor knockout mice display osteopenia with reduced bone formation and enhanced bone resorption. J Endocrinol 2010; 207(3):257-63.
61. Retraction for Igarashi et al., Vitamin K induces osteoblast differentiation through pregnane X receptor-mediated transcriptional control of the Msx2 gene. Mol Cell Biol 2014; 34(5):918.
62. Blair HC, Larrouture QC, Li Y, et al. Osteoblast differentiation and bone matrix formation in vivo and in vitro. Tissue Eng Part B Rev 2017; 23(3):268-80.
63. Yamaguchi M, Ma ZJ. Inhibitory effect of menaquinone-7 (vitamin K2) on osteoclast-like cell formation and osteoclastic bone resorption in rat bone tissues in vitro. Mol Cell Biochem 2001; 228(1-2):39-47.
64. Kim M, Na W, Sohn C. Vitamin K1 (phylloquinone) and K2 (menaquinone-4) supplementation improves bone formation in a high-fat diet-induced obese mice. J Clin Biochem Nutr 2013; 53(2):108-13.
65. Yamauchi M, Yamaguchi T, Nawata K, Takaoka S, Sugimoto T. Relationships between undercarboxylated osteocalcin and vitamin K intakes, bone turnover, and bone mineral density in healthy women. Clin Nutr 2010; 29(6):761-65.
66. Yamaguchi M. Role of nutritional factor menaquinone-7 in bone homeostasis and osteoporosis prevention. Integr Mol Med 2014; 1(1):1-6.
67. Wu WJ, Kim MS, Ahn BY. The inhibitory effect of vitamin K on RANKL-induced osteoclast differentiation and bone resorption. Food Funct 2015; 6(10):3351-58.
68. Taylor PM. Role of amino acid transporters in amino acid sensing. Am J Clin Nutr 2014; 99(1):223S-230S.
69. Jewell JL, Russell RC, Guan K-L. Amino acid signalling upstream of mTOR. Nat Rev Mol Cell Biol 2013; 14(3):133-39.
70. Jia G, Aroor AR, Martinez-Lemus LA, Sowers JR. Overnutrition, mTOR signaling, and cardiovascular diseases. Am J Physiol Regul Integr Comp Physiol 2014; 307(10):R1198-R1206.
71. Greider CW. Regulating telomere length from the inside out: the replication fork model. Genes Dev 2016; 30(13):1483-91.
72. Völkers M, Doroudgar S, Nguyen N, et al. PRAS40 prevents development of diabetic cardiomyopathy and improves hepatic insulin sensitivity in obesity. EMBO Mol Med 2014; 6(1):57-65.
73. Samuel VT, Shulman GI. Mechanisms for insulin resistance: common threads and missing links. Cell 2012;148(5):852-871.
74. Han J, Li E, Chen L, et al. The CREB coactivator CRTC2 controls hepatic lipid metabolism by regulating SREBP1. Nature 2015; 524(7564):243-246.
75. Cornu M, Oppliger W, Albert V, et al. Hepatic mTORC1 controls locomotor activity, body temperature, and lipid metabolism through FGF21. Proc Natl Acad Sci 2014; 111(32):11592-99.
76. Passtoors WM, Beekman M, Deelen J, et al. Gene expression analysis of mTOR pathway: association with human longevity. Aging Cell 2013; 12(1):24-31.
77. Engelman JA, Luo J, Cantley LC. The evolution of phosphatidylinositol 3-kinases as regulators of growth and metabolism. Nat Rev Genet 2006; 7(8):606-19.

78. Chalhoub N, Baker SJ. PTEN and the PI3-kinase pathway in cancer. Annu Rev Pathol 2009; 4:127-50.
79. Um SH, Frigerio F, Watanabe M, et al. Absence of S6K1 protects against age- and diet-induced obesity while enhancing insulin sensitivity. Nature 2004; 431(7005):200-5.
80. Thedieck K, Holzwarth B, Prentzell MT, et al. Inhibition of mTORC1 by astrin and stress granules prevents apoptosis in cancer cells. Cell 2013; 154(4):859-874.
81. Melnik BC, John S, Carrera-Bastos P, Cordain L. The impact of cow's milk-mediated mTORC1-signaling in the initiation and progression of prostate cancer. Nutr Metab 2012; 9(1):74.
82. Chang L, Chiang SH, Saltiel AR. Insulin signaling and the regulation of glucose transport. Mol Med 2004; 10(7-12):65-71.
83. Uno K, Yamada T, Ishigaki Y, et al. A hepatic amino acid/mTOR/S6K-dependent signalling pathway modulates systemic lipid metabolism via neuronal signals. Nat Commun 2015; 6:7940.
84. Ali M, Bukhari SA, Ali M, Lee HW. Upstream signalling of mTORC1 and its hyperactivation in type 2 diabetes (T2D). BMB Rep 2017; 50(12):601-9.
85. Martelli AM, Buontempo F, McCubrey JA. Drug discovery targeting the mTOR pathway. Clin Sci 2018; 132(5):543-68.
86. Jiang M, Fu X, Yang H, Long F, Chen J. mTORC1 signaling promotes limb bud cell growth and chondrogenesis. J Cell Biochem 2017; 118(4):748-53.
87. Xian L, Wu X, Pang L, et al. Matrix IGF-1 maintains bone mass by activation of mTOR in mesenchymal stem cells. Nat Med 2012; 18(7):1095-101.
88. Chen J, Tu X, Esen E, et al. WNT7B promotes bone formation in part through mTORC1. PLoS Genet 2014; 10(1):e1004145.
89. Karner CM, Esen E, Okunade AL, Patterson BW, Long F. Increased glutamine catabolism mediates bone anabolism in response to WNT signaling. J Clin Invest 2015; 125(2):551-62.
90. Karner CM, Lee S-Y, Long F. Bmp Induces Osteoblast Differentiation through both Smad4 and mTORC1 Signaling. Mol Cell Biol 2017; 37(4):e00253-16.
91. Lim J, Shi Y, Karner CM, et al. Dual function of Bmpr1a signaling in restricting preosteoblast proliferation and stimulating osteoblast activity in mouse. Development 2016; 143(2):339-47.
92. Wu Y, Chhipa RR, Cheng J, Zhang H, Mohler JL, Ip C. Androgen receptor-mTOR crosstalk is regulated by testosterone availability: implication for prostate cancer cell survival. Anticancer Res 2010; 30(10):3895-901.
93. Xu G, Li Z, Ding L, et al. Intestinal mTOR regulates GLP-1 production in mouse L cells. Diabetologia 2015; 58(8):1887-97.
94. 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.
95. 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; 17(8):2617.
96. Tumedei M, Piattelli A, Degidi M, Mangano C, Iezzi G. A narrative review of the histological and histomorphometrical evaluation of the peri-implant bone in loaded and unloaded dental implants. A 30-year experience (1988-2018). Int J Environ Res Public Health 2020; 17(6):2088.
97. Fanali S, Tumedei M, Pignatelli P, et al. Implant primary stability with an osteocondensation drilling protocol in different density polyurethane blocks. Comput Methods Biomech Biomed Engin 2020; 2020:1-7.
98. Fujiwara S, Kato S, Bengazi F, et al. Healing at implants installed in osteotomies prepared either with a piezoelectric device or drills: an experimental study in dogs. Oral Maxillofac Surg 2021; 25(1):65-73.
99. Kotsu M, Urbizo Velez J, Bengazi F, et al. Healing at implants installed from ~70- to <10-Ncm insertion torques: an experimental study in dogs. Oral Maxillofac Surg 2021; 25(1):55-64.
100. Cao X, Liu XM, Zhou LH. Recent progress in research on the distribution and function of NUCB2/nesfatin-1 in peripheral tissues. Endocr J 2013; 60(9):1021-27.
101. Takagi K, Miki Y, Tanaka S, et al. Nucleobindin 2 (NUCB2) in human endometrial carcinoma: a potent prognostic factor associated with cell proliferation and migration. Endocr J 2016; 63(3):287-99.
102. Scarano A, Sinjari B, Murmura G, Lorusso F.

Neurosensory disturbance of the inferior alveolar nerve after 3025 implant placements. Implant Dent 2017; 26(5):735-43.
103. Saito M, Kida Y, Kato S, Marumo K. Diabetes, Collagen, and Bone Quality. Curr Osteoporos Rep 2014; 12(2):181-88.
104. Bluher M. Extended longevity in mice lacking the insulin receptor in adipose tissue. Science 2003; 299(5606):572-74.
105. Blüher M, Michael MD, Peroni OD, et al. Adipose tissue selective insulin receptor knockout protects against obesity and obesity-related glucose intolerance. Dev Cell 2002; 3(1):25-38.
106. Katic M, Kennedy AR, Leykin I, et al. Mitochondrial gene expression and increased oxidative metabolism: role in increased lifespan of fat-specific insulin receptor knock-out mice. Aging Cell 2007; 6(6):827-839.
107. Brown-Borg HM, Borg KE, Meliska CJ, Bartke A. Dwarf mice and the ageing process. Nature 1996; 384(6604):33-33.
108. Flurkey K, Papaconstantinou J, Miller RA, Harrison DE. Lifespan extension and delayed immune and collagen aging in mutant mice with defects in growth hormone production. Proc Natl Acad Sci 2001; 98(12):6736-6741.
109. Chandrashekar V, Bartke A, Coschigano KT, Kopchick JJ. Pituitary and testicular function in growth hormone receptor gene knockout mice. Endocrinology 1999; 140(3):1082-88.
110. Bartke A. Insulin and aging. Cell Cycle 2008; 7(21):3338-43.
111. Taniguchi CM, Emanuelli B, Kahn CR. Critical nodes in signalling pathways: insights into insulin action. Nat Rev Mol Cell Biol 2006; 7(2):85-96.
112. Besson A, Salemi S, Gallati S, et al. Reduced longevity in untreated patients with isolated growth hormone deficiency. J Clin Endocrinol Metab 2003; 88(8):3664-67.
113. Shevah O, Laron Z. Patients with congenital deficiency of IGF-I seem protected from the development of malignancies: a preliminary report. Growth Horm IGF Res 2007; 17(1):54-57.
114. Bonafè M, Barbieri M, Marchegiani F, et al. Polymorphic variants of insulin-like growth factor I (IGF-I) receptor and phosphoinositide 3-kinase genes affect IGF-I plasma levels and human longevity: cues for an evolutionarily conserved mechanism of life span control. J Clin Endocrinol Metab 2003; 88(7):3299-3304.
115. Cantore S, Mirgaldi R, Ballini A, et al. Cytokine gene polymorphisms associate with microbiogical agents in periodontal disease: our experience. Int J Med Sci 2014; 11(7):674-79.
116. Ballini A, Gnoni A, De Vito D, et al. Effect of probiotics on the occurrence of nutrition absorption capacities in healthy children: a randomized double-blinded placebo-controlled pilot study. Eur Rev Med Pharmacol Sci 2019; 23(19):8645-57.
117. Dato S, Soerensen M, De Rango F, et al. The genetic component of human longevity: New insights from the analysis of pathway-based SNP-SNP interactions. Aging Cell 2018; 17(3):e12755.
118. Van Heemst D. Insulin, IGF-1 and longevity. Aging Dis 2010; 1(2):147-57.
119. Lago CU, Sung HJ, Ma W, Wang P, Hwang PM. P53, aerobic metabolism, and cancer. Antioxid Redox Signal 2011; 15(6):1739-48.
120. Sena LA, Chandel NS. Physiological roles of mitochondrial reactive oxygen species. Mol Cell 2012; 48(2):158-167.
121. Sádaba MC, Martín-Estal I, Puche JE, Castilla-Cortázar I. Insulin-like growth factor 1 (IGF-1) therapy: Mitochondrial dysfunction and diseases. Biochim Biophys Acta 2016; 1862(7):1267-78.
122. Velarde MC. Mitochondrial and sex steroid hormone crosstalk during aging. Longev Healthspan 2014; 3(1):2.
123. Góralska J, Śliwa A, Gruca A, et al. Glucagon-like peptide-1 receptor agonist stimulates mitochondrial bioenergetics in human adipocytes. Acta Biochim Pol 2017; 64(3):423-429.
124. Kukat C, Davies KM, Wurm CA, et al. Cross-strand binding of TFAM to a single mtDNA molecule forms the mitochondrial nucleoid. Proc Natl Acad Sci 2015; 112(36):11288-93.
125. Wong TS, Rajagopalan S, Freund SM, et al. Biophysical characterizations of human mitochondrial transcription factor A and its binding to tumor suppressor p53. Nucleic Acids Res 2009; 37(20):6765-83.
126. Croteau DL, Rossi ML, Canugovi C, et al. RECQL4

localizes to mitochondria and preserves mitochondrial DNA integrity: RECQL4 in mitochondria. Aging Cell 2012; 11(3):456-466.

127. Geraldes P, King GL. Activation of protein kinase C isoforms and its impact on diabetic complications. Circ Res 2010; 106(8):1319-31.
128. Guo N, Parry EM, Li LS, et al. Short telomeres compromise β-cell signaling and survival. PLoS One 2011; 6(3):e17858.
129. Andreasen AS, Kelly M, Berg RMG, Møller K, Pedersen BK. Type 2 diabetes is associated with altered NF-κB DNA binding activity, JNK phosphorylation, and AMPK Phosphorylation in Skeletal Muscle after LPS. PLoS One 2011; 6(9):e23999.
130. Chung SS, Wu Y, Okobi Q, et al. Proinflammatory cytokines IL-6 and TNF- α increased telomerase activity through NF- κ B/STAT1/STAT3 activation, and withaferin A inhibited the signaling in colorectal cancer cells. Mediators Inflamm 2017; 2017:5958429.
131. Morrisette-Thomas V, Cohen AA, Fülöp T, et al. Inflamm-aging does not simply reflect increases in pro-inflammatory markers. Mech Ageing Dev 2014; 139:49-57.
132. De Martinis M, Franceschi C, Monti D, Ginaldi L. Inflammation markers predicting frailty and mortality in the elderly. Exp Mol Pathol 2006; 80(3):219-27.
133. Nitta E, Yamashita M, Hosokawa K, et al. Telomerase reverse transcriptase protects ATM-deficient hematopoietic stem cells from ROS-induced apoptosis through a telomere-independent mechanism. Blood 2011; 117(16):4169-80.
134. Yin L, Hubbard AK, Giardina C. NF-κB regulates transcription of the mouse telomerase catalytic subunit. J Biol Chem 2000; 275(47):36671-75.
135. Xu D, Erickson S, Szeps M, et al. Interferon α down-regulates telomerase reverse transcriptase and telomerase activity in human malignant and nonmalignant hematopoietic cells. Blood 2000; 96(13):4313-18.
136. Viceconte N, Dheur M-S, Majerova E, et al. Highly aggressive metastatic melanoma cells unable to maintain telomere length. Cell Rep 2017; 19(12):2529-43.
137. Balzanelli GM, Distratis P, Amatulli F, et al. Clinical features in predicting COVID-19. Biomed J Sci Tech Res 2020; 29(5):22921-26.
138. Nguyen KC, Balzanelli MG, Distratis P, et al. Could immunity boosting therapy help COVID-19 patient? Biomed J Sci Tech Res 2020; 30(1):23149-50.
139. Balzanelli GM, Distratis P, Aityan SK, et al. COVID-19 and COVID-like patients: a brief analysis and findings of two deceased cases. Maced J Med Sci 2020; 8(T1):490-95.
140. Balzanelli MG, Distratis P, Catucci O et al. Clinical and diagnostic findings in COVID-19 patients: an original research from SG Moscati Hospital in Taranto Italy. J Biol Regul Homeost Agents 2021; 35(1):171-83.
141. Balzanelli GM, Distratis P, Amatulli F et al. Would the end of COVID-19 infection as a chronic disease? J Stem Cells Res Dev Ther 2020; 6:057.