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Research Article

# Body Kines and Organ Crosstalks: A Mini Review

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## Abstract

Multiple organs are recently being recognized as having endocrine functions through their release of different hormones and proteins that are responsible for biologically interrelated and inter-connected signaling processes. Diabetes and other chronic diseases are subject to be influenced by these products where modulation or change of their function could take place due to alterations in the signaling processes affected by the secretion of these products In this mini review we tried to take a closer look at how these proteins referred to as “kines” which are considered as the leaders of communication will help the crosstalk between different tissues and it is of utmost important to discover in what way they can do that,. We will review the multiple and complex ways by which kines affect the physiological and pathological processes through reviewing what had been published of the works dealing with the action of different kines and what are the main organs that produce them although a great number of them had not yet been discovered or studied exclusively. The deep identification of their roles in health and diseases will pave the way for the pharmaceutical industry to innovate new drugs that will target their action towards a better organ harmony for the benefits of the patients.

## Keywords

Kines, Myokines, Adiponectin, Osteocalcine, Hepatokines, Insulin Resistance

## 1. Introduction

Diabetes is a very complex disorder that is associated with a large number of complications and end-organ disease processes in people afflicted with the disease. There are numerous pathogenetic mechanisms that contribute to the development of the full clinical picture and the subsequent complications. There is still a significant number of unknowns surrounding these processes that are being currently researched, and every next day we know better about the old and newly discovered mechanisms behind this syndrome.

Over the past 50 years, continued research of molecular biology has led to a deepened understanding of developmental and post-natal processes occurring in our species. These advances in our understanding of molecular biology had reshaped the way we think about the biological interrelated and inter-connected processes, that control the way our systems communicate. Such communication happens through the secretion of molecules which help signaling to other organs which in turn secretes other molecules to complete the cycle [1].

Spiegelman and Flier laboratories in 1987 were the first to

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start describing these communicative processes [2], they were pioneers in defining adipose tissue as an endocrine organ based on their finding that these cells secrete a protein which they called, adipsin which exerts its action by signaling other tissues. Friedman and his colleagues [3], had a landmark finding in which they identified another secretory protein called leptin secreted from adipose tissue. Not so long after, various other proteins were discovered and the list of adipokines (hormones secreted from adipose tissue) had expanded to include many new members including, for example, adiponectin, resistin, and visfatin [4, 5].

However, the realization that muscles also can secrete similar proteins deepened after the discovery of a muscle-derived IL-6 (interleukin-6) [6] which led to the coining up of the term "myokines" in 2003 [7], had pointed out to this finding through the work of many other research groups studying hundreds of "kines" produced by other organs. These organs were recognized to have an endocrine function and their actions were carried out through rather different routes [8, 9], and one of these exciting examples are the endocrine functions of bone and striated muscles.

## 2. Bone as an Endocrine Organ

Research around osteoblasts, the main bone forming cells, showed that they increase the expression of Insulin in pancreatic islets and of Adiponectin in adipocytes. Conversely, Fibroblasts, which are intimately related to osteoblasts, did not show a similar effect on Insulin or Adiponectin expression. It was found that only Insulin and Adiponectin expression is affected by the supernatant of osteoblast cultures [10-13].

Osteocalcin, a protein secreted only by osteoblasts, is one of the "kines" that affect such processes. It exists in two forms; a carboxylated form that is inactive and bound to bone, and an uncarboxylated form that leads to an increased Insulin and Adiponectin expression in their respective organs [14] (figure 1, 2).

Thus, it was clear that osteocalcin is a bone-derived hormone that regulates β-cell proliferation, Insulin expression and insulin secretion in both mice and humans. Uncarboxylated and not the carboxylated osteocalcin was shown to promote insulin secretion and stimulated β-cell proliferation in the Islets of Langerhans. It has been also linked to a reduction in visceral fat accumulation including liver fat accumulation. Osteocalcin has other roles as it was shown to have a role in testosterone production and glucagon-like peptide-1 synthesis as demonstrated in the figures below. Further actions involve muscle-bone crosstalk and has a role in cognitive function. (Figures 3, 4). A growing body of evidence suggests a link between osteocalcin and neurological disorders, but this relationship is not fully understood as of yet.

It seems that Osteocalcin can regulate myelination in oligodendrocytes and may affects the thickness of myelin surrounding neurons. It regulates a variety of neuronal activities related to cognition and anxiety, such as neurotransmitter synthesis, synaptic plasticity, brain - derived neurotrophic factor synthesis, neurogenesis, and autophagy [9].

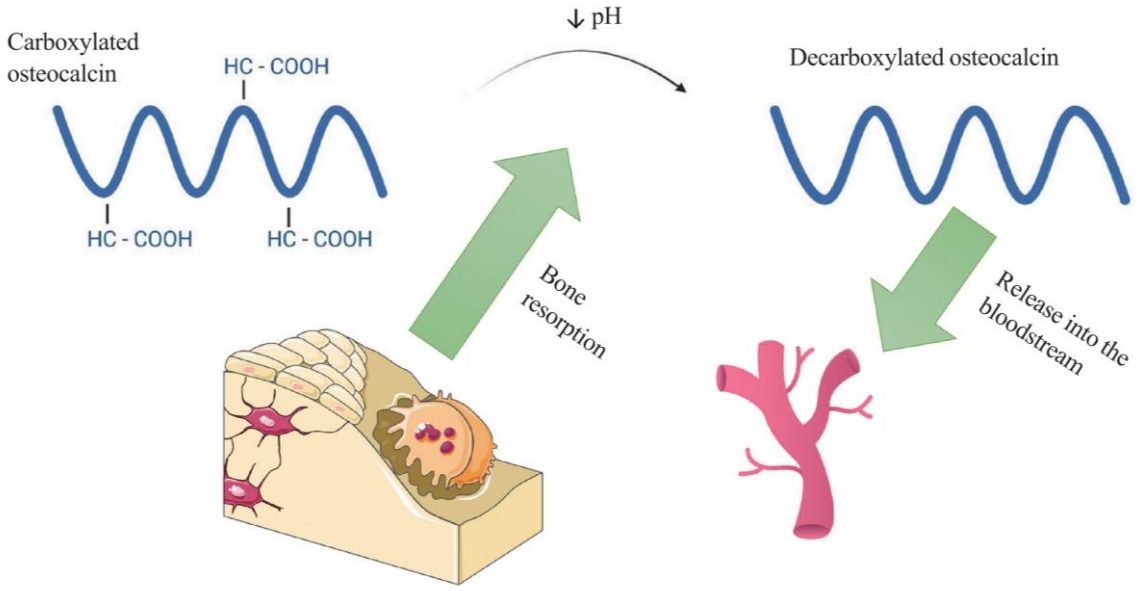


***Figure 1.*** *The differential action of both forms of osteocalcin.*

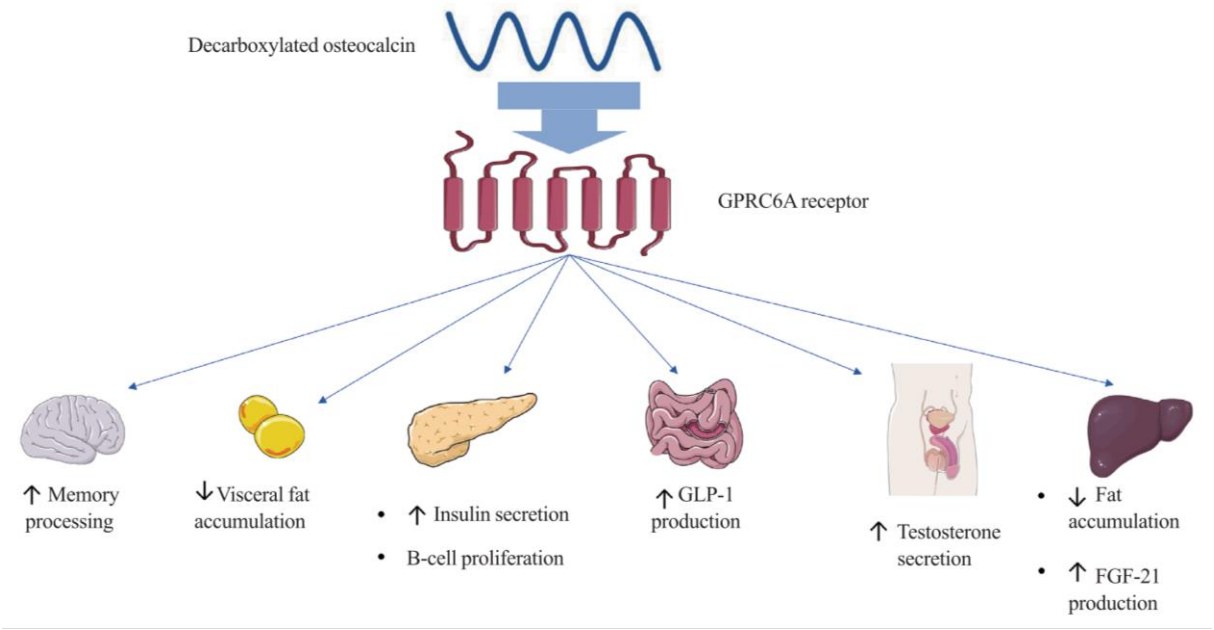


***Figure 2.*** *The actions of the decarboxylated form of osteocalcin.*

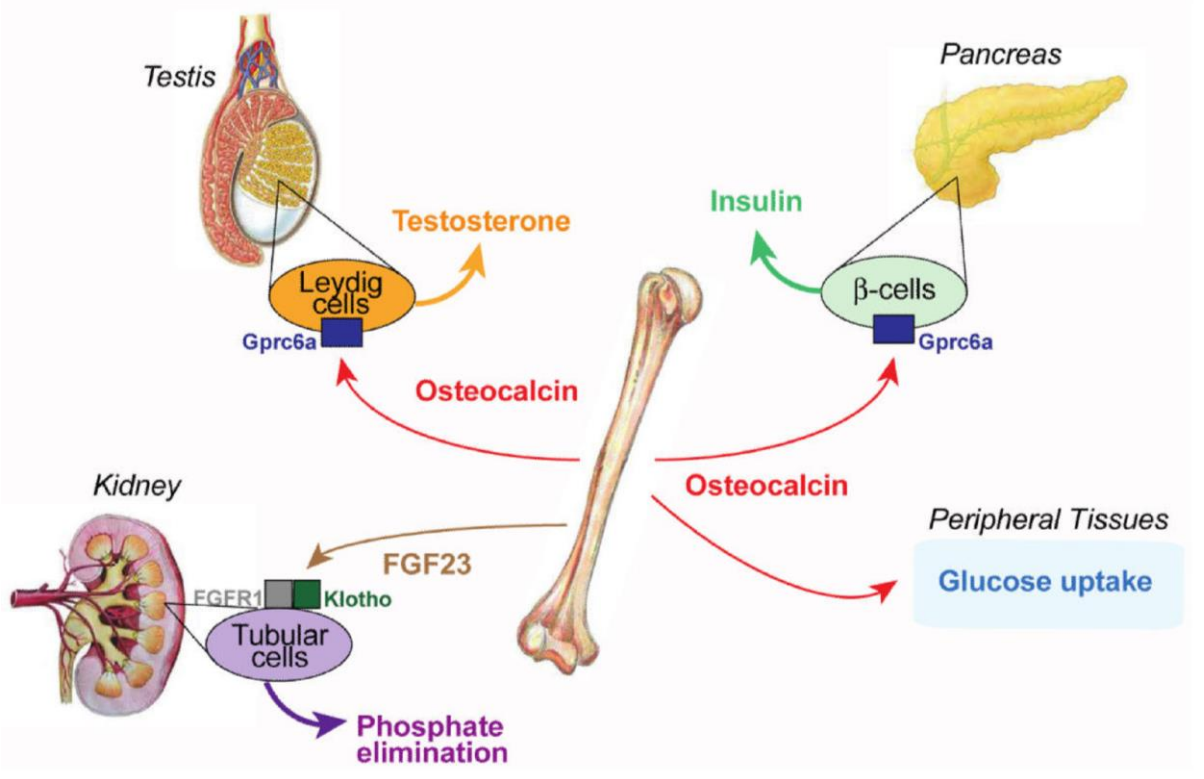


***Figure 3.*** *Pathways of the different actions of osteocalcin.*

Mice deficient in osteocalcin genes are generally characterized by hyperglycemia, a reduction in insulin secretion, increased visceral fat, a reduction in lean mass, smaller testes and lower blood testosterone levels than wild-type (WT) mice [15].

In mice, the osteocalcin GPRC6A receptor was found in other cells, such as the liver, bone, small intestine, brain, skeletal muscles and the testes. This indicates that osteocalcin may have a role in modulating the functions of these organs [16]. Mice deficient in GPRC6A expression in hepatocytes had an increased hepatic fat accumulation and glycogen depletion. They also demonstrated an impaired glucose tolerance.

One of the most important findings of the study of the en-

docrine functions of osteocalcin was the identification of its role in the muscle-bone feedback loop (muscle-bone crosstalk) [17] Mera et al [18] found that Osteocalcin signaling in the myofibers of mice is necessary and sufficient for optimum adaptation to exercise and that serum osteocalcin concentrations increased after exercise. However, this effect reduced with increasing age. Injecting osteocalcin immediately before exercise was found to increase the exercise capacity of young mice. It also restored exercise capacity to basal levels found in young mice when injected in older mice. Long term osteocalcin injection increased lean muscle mass in mice [19].

Osteocalcin was found to increase the release of interleukin-6 (IL-6) by myofibers. In turn, IL-6, which is produced by muscle fibers during exercise, promotes bone resorption, which increases serum osteocalcin concentrations [20, 21].

Additionally, Oury et al. [22] had demonstrated that osteocalcin crosses the blood-brain barrier and influences the expression of the tryptophan hydroxylase-2 (Tph2), tyrosine hydroxylase (Th), glutamate decarboxylase-1 (Gad1), and Gad2 genes, which affects neurotransmitter concentrations. This leads to behavioral changes, impaired memory, anxiety and slow learning. It was found that physical activity decreases the rate of cognitive decline in healthy people and in people with neurodegenerative disorders (Figure 4).

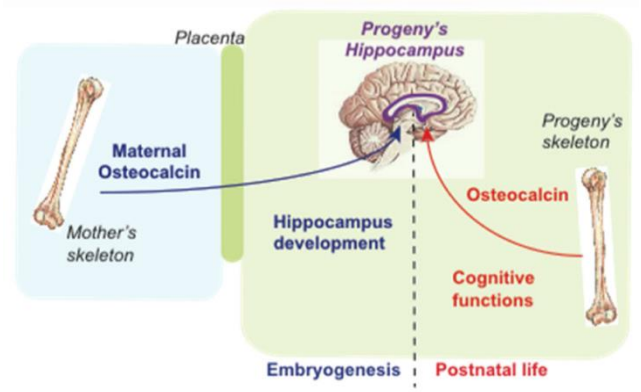


***Figure 4.*** *The effects of osteocalcin on cognitive functions in postnatal life.*

Bone secretes other hormones that are proven to have other functions related remotely to other organs, Fibroblast growth factor 23 (FGF23) is one of these hormones, produced mainly by osteocytes and osteoblasts [23, 24]. It is involved in the regulation of phosphate metabolism and Vitamin D synthesis in the kidneys. Increased activity of FGF23 can lead to the development of rare forms of rickets and hypophosphatemic osteomalacia, such as X-chromosome-associated hypophosphatemia and tumour-induced osteomalacia [25, 26].

Recently, another hormone called sclerostin, was found to have endocrinal functions as well in the form of regulation of energy metabolism. Lipocalin 2 is another hormone linked to the regulation of glucose metabolism.

*Skeletal Muscle as Endocrine Tissue*

Skeletal muscle has also been identified as an important endocrine organ. Research in past two decades has shown that skeletal muscle can produce and secrete a myriad of myokines that exert their effects in either an autocrine, paracrine, or endocrine manner. Signaling from muscles to other tissues often occurs as a result of muscle contraction which helps determine energy expenditure in distal tissues. Balancing the metabolism across the body through communication between the brain, muscle, adipose tissues and the liver is key for energy regulation. Increased physical activity decreases lessens the risk of multiple diseases and pathologic processes such as type 2 diabetes, dementia, cardiovascular diseases, and some forms of cancer.

Only 5% of all known myokines have had their biological function identified. The concept of the myokinome has helped shape the understanding by which mechanisms muscles exert these effects on distal tissues [27].

Myostatin was the first identified muscle derived factor that fulfils the myokine criteria [28]. Myostatin is one of the transforming growth factor β (TGF-β) superfamily and negatively regulates myogenesis in an autocrine manner (Figure 5).

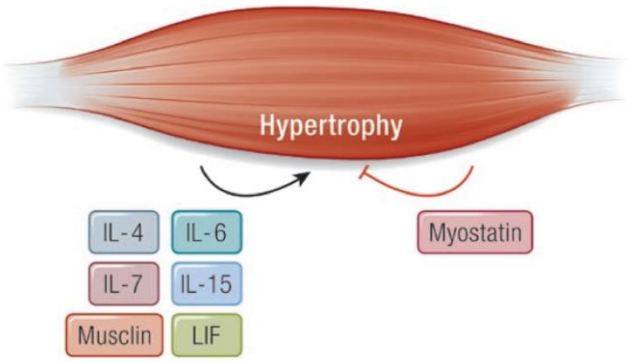


***Figure 5.*** *Source: Endocrine Reviews, August 2020, 41(4): 594–609 5. Unrestricted reuse of the figures (Attribution License)(http://creativecommons.org/licenses/by/4.0/), which permits unrestricted reuse, distribution, and reproduction in any medium).*

Decorin has been identified as an antagonist to myostatin and it is regulated by exercise. Decorin levels increase post-exercise as opposed to a reduction in myostatin levels within muscles and blood [29-31].

IL-6 plays an important role in myogenesis, apart from its well-known effects on lipid and glucose metabolism. Other myokines, including IL-15 and IL-7 [32, 33] have also been shown to influence muscle formation in mice [34, 35] (Figure 6).

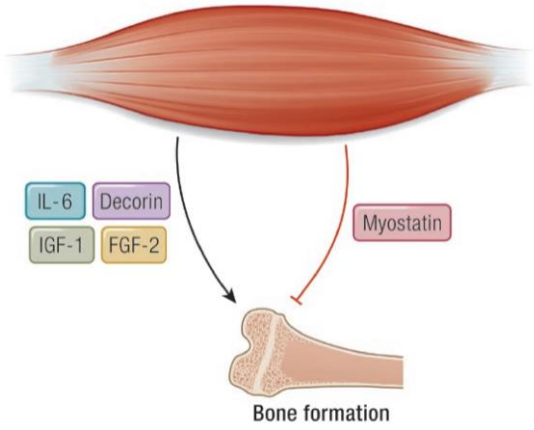


***Figure 6.*** *Decorin, IL-6, IGF-1, and FGF-2 positively regulate bone formation. Abbreviations: FGF-2, firoblast growth factor 2; IGF-1, insulin-like growth factor I. Endocrine Reviews, August 2020, 41(4): 594–609.*

## 3. Muscle–Liver & Gut Crosstalk

During exercise, an increased glucose uptake in muscle went hand in hand with increased glucose production from the liver to maintaing glucose homeostasis. This glucose production from the liver is stimulated by the release of IL-6 [36].

IL-6 was also shown to increase GLP-1 secretion that in turn improves insulin production and sensitivity. This strengthens the hypothesis relating IL-6 in the regulation of insulin secretion. As such, IL-6 may play a part in an "endocrine loop" protecting against impaired glucose homeostasis. Lehroskv et al, [37] observed the effect of IL-6 on postprandial glycemia and insulin secretion. They concluded that IL-6 delays gastric emptying, which significantly impacts postprandial glucose levels [38].

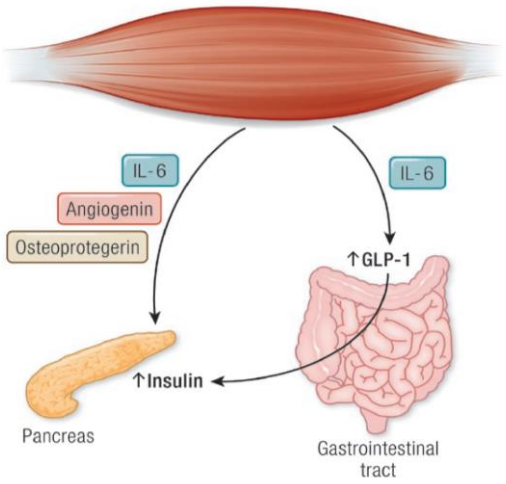


***Figure 7.*** *Severinsen and Pedersen Myokines in Muscle–Organ Crosstalk Endocrine Reviews, August 2020, 41(4): 594–609.*

It has positively shown that IL-6 can impact β-cell mass in vivo through activating β-cell proliferation and preventing apoptosis [39]. This may lead to the proposition that increased IL-6 levels in response to exercise can be involved in protecting pancreatic β-cell mass and function (Figure 7).

## 4. Cardiokines and CVS

Another exciting area of research had shown that a factor known as FSTL1 which is considered as a cardiokine possesses cardioprotective effcts, improving endothelial cell function and revascularization in animal models post-cardiac insult by way of nitric oxide synthase [40, 41]. High concentrations of FSTL1 are seen in patients with heart failure [42]. As such, FSTL1 levels can have prognostic signifiance in acute coronary syndromes [43]. A study conducted on canines in vivo showed that FSTL1 can improve myocardial substrate metabolism [44].

## 5. Myokines as Anti-Inflammory Substances

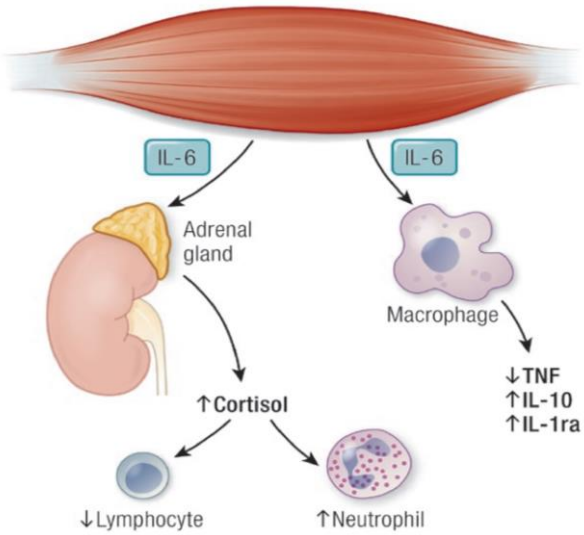


***Figure 8.*** *source: https://academic.oup.com/edrv. doi: 10.1210/endrev/bnaa016.*

In human beings, it was found that exercise induces anti-inflammatory effects both in a short term and long term manner. Long term training adaptation is also associated with a reduction in abdominal adiposity. Acute increases in IL-6 post and during exercise promote multiple systemic anti-inflammatory effects. IL-6 stimulates the increased production of other anti-inflammatory cytokines namely, IL-1 receptor antagonist (IL-1ra) and IL-10 [45]. IL-1ra inhibits IL-1β signal transduction, while IL-10 inhibits synthesis of TNF-α [46, 47]. Not to mention the reduction in visceral and cardiac fat mass associated with exercise training [48-51]. (Figure 8).

## 6. Myokines and "Other Kines": Adipokines, Hepatokines and Batokines

Hepatokines have been recently recognized as a novel group of liver-derived exercise factors. They include FGF-21, follistatin, angiopoietin-like protein 4, heat shock protein 72, and IGF binding protein. These are released from the liver during or immediately after a bout of exercise [52]. Muscle contraction leads to the release of these hepatokines and seem to be involved in mediating some of the metabolic effects of exercise. Other "kines" are now being recognized with the identification of classic brown adipose tissue in adult humans [53], which led to the idea of "Batokines". Proteomic-based identification has helped classify 101 proteins as brown, rather than white, adipocyte tissue [54]. The focus remains mostly on myokines and hepatokines when it comes to mediating exercise-induced muscle crosstalk.

Lack of physical activity is associated with a myriad of diseases, including type 2 diabetes, cardiovascular diseases, cancer, dementia, and osteoporosis. The negative effects associated with a sedentary lifestyle might be mediated by a lack of myokine release and/or resistance to the effects of some of them [55].

Novel therapeutic targets for all these diseases mentioned above can be identified by further study of myokines (Figures 9, 10).

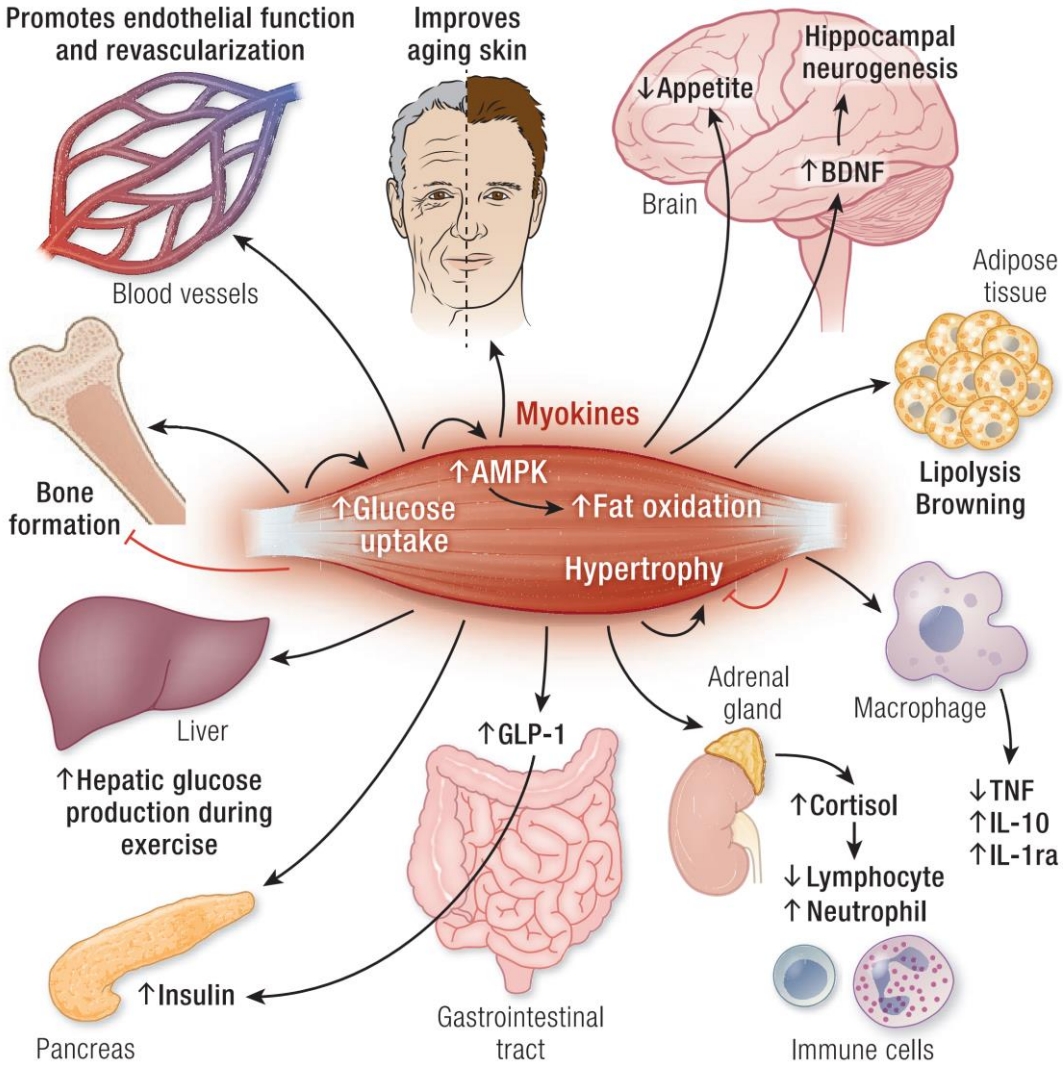


***Figure 9.*** *Source: (Endocrine Reviews 41: 594 – 609, 2020) (Attribution License (http:// creativecommons.org/ licenses/by/4.0/), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited).*

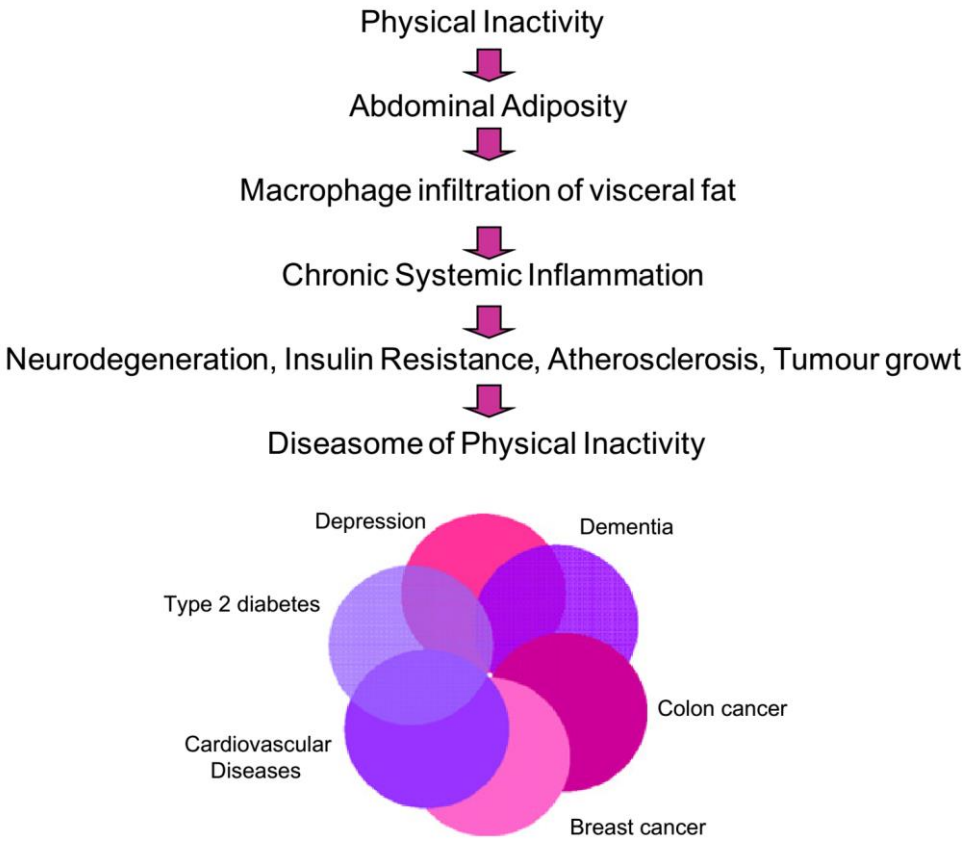


***Figure 10.*** *Source: Brain, Behavior, and Immunity 25 (2011) 811–816.*

## 7. Conclusions

It is becoming clear that organs can deal with each other in harmony to cooperate in controlling vital processes that are frequently required to supervise and control the normal metabolic processes apart from other functional performances. At least up until now, we have discovered over 500 different kines secreted from the muscles, adipose tissue, the liver, the heart and other organs that will communicate together to form a network of completely interrelated biological processes. The list of adipokines for example had expanded to include many new members including, for example, adiponectin, resistin, and visfatin and others and every new day we discover more and more. The identification of these kines and studying of their roles in the human body can give way to new therapeutic options for many diseases.

## Abbreviations

| | |
|---|---|
| GPRC6A | Osteocalcin Receptor |
| IL-6 | Interleukin-6 |
| Tph2 | Tryptophan Hydroxylase-2 |
| Th | Tyrosine Hydroxylase |
| Gad1-Gad2 | Glutamate Decarboxylase1&2 |

## Conflicts of Interest

The authors declare no conflicts of interest.

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