

## Review Article

# A Review on Metabolic Paradoxes and their Impact on Metabolism

Gasmi, A<sup>1\*</sup>, Piscopo, S<sup>1,2</sup>, Menzel, A<sup>3</sup>, Noor, S<sup>4</sup>

1. *Société Francophone de Nutrithérapie et de Nutrigénétique Appliquée, Villeurbanne, France*

2. *Research and Development Departement, Nutri-Logics SA, Weiswampach, Luxembourg*

3. *Laboratoires Réunis, Junglinster, Luxembourg*

4. *Institute of Molecular Biology and Biotechnology, Bahauddin Zakariya University Multan, Pakistan*

Received 12 October 2021; Accepted 5 November 2021

Corresponding Author: dr.amin.gasmi@gmail.com

---

### Abstract

The current review paper portrays the important link of different nutrients like trace elements, proteins, fatty acids, vitamins, and amino acids with the immune system as well as information related to metabolic paradoxes. Optimum working of the metabolic system is essential because it gives various types of supplements to the human body and aid in chemical pathways. Here related data have been retrieved from two databases i.e., PubMed and Google scholar to grasp detailed knowledge about micronutrients and nutrients as well as their association in the metabolic system. Like protein play important role in the normal development of different immune components, amino acids including alanine, Arginine, and glutamic acid properly control the movement of neutrophils, macrophages, and cytokines. While fatty acids act as an anti-inflammatory agent because they possess the ability to inhibit the expression of the MHC class. Apart from these, many essential molecules like uric acid, proteins, calcium, lanolin are also obtained as end products after catabolic and anabolic reactions, and it was found that the uric acid paradox has a cancer inhibitory role. Additionally, TGF and IL-6 paradoxes have a role in the development of tumors, the onset of diabetes, and low-grade inflammatory disorders respectively. However, the entire functioning of metabolic processes depends upon daily diet because humans get the important nutrient from the diet which further vital role in the immune system. Moreover, it was also observed that calcium paradox is related to heart disorders because high calcium accumulation leads to cardiac disorders. Thus, the complete knowledge about these essential components as well as metabolic paradoxes is very important due to their antagonistic role to plan better and improved therapeutic strategies for various diseases.

**Keywords:** metabolism, vitamin C, uric acid, exercise, glutamine

---

### 1. Context

The term metabolism can be defined as the series of chemical reactions that take place every time in living organisms to maintain their living standards properly. These metabolic processes are further classified into catabolism and anabolism. The breakdown of the molecular structure of glucose for the attainment of energy, which is further utilized by the human body for various tasks, is known as

catabolism while anabolism involves the formation of the essential molecules that are necessary for the optimum working of an individual cell (1). Metabolic processes are a major source of providing essential supplements to the human body which helps in nourishment. Additionally, it can also be described as the chemical pathways that take place in the cells of the human body to attain vitality. In a living organism, the process of metabolism entirely

depends upon the diet that is consumed by an individual because all the dietary components then break down into smaller molecules for the production of energy in humans (2). Thus, basic supplements that the body needs are majorly provided by a healthy balanced diet because certain essential elements cannot be synthesized in the body as well as they provide a group of important substances like protein, lipids, minerals, and sugar that play a key role in maintaining the normal structure of the cell, to repair the damaged body tissues as well as helps to ensure the overall optimum working of the body (3). Carbohydrates are accumulated within the body through the consumption of sugar; starch and cellulose because it fulfills the need for glucose that can further metabolize for synthesizing energy for the body to carry out its activities. Protein is one of the most important components that are responsible for the proper development of tissues in the body of organisms (4). Protein is essential for the formation and maintenance of the cell structure, for the development of hemoglobin which transports oxygen, as well as proteins, are also imperative because they are a major source of nitrogen that is utilized for the hereditary material. Thus, proteins are fundamental for the survival of an organism because they contain different types of essential and non-essential amino acids (5). Protein can be obtained from different dietary sources including meats, vegetables, grains, and dairy products. "Paradox" can be characterized as an "opposing articulation or logically self-contradictory statements that possess valid reasoning from true premises but lead to a seemingly logically unacceptable conclusion (6).

The purpose of this review article is to study the significant association of different nutrients like trace elements, proteins, fatty acids, vitamins, and amino acids with the metabolism as well information related to metabolic paradoxes. It has also been described that how these nutrients can be involved in progression of

different diseases which will help researcher to devise new treatment strategies against such diseases.

## 2. Evidence Acquisition

Almost complete search of medical databases including PubMed, Scopus, and Google Scholar was done to gather relevant information. Keywords like "Trace elements AND Metabolism", "Proteins AND Metabolism", "Vitamins AND Metabolism" were used. In order to extract particular research articles on the subject of metabolic paradoxes as well amino acids, proteins, and trace elements the names of these nutrients were put in the research bar to retrieve relevant research papers. Here the exclusion and inclusion criteria were applied to narrow down only those relevant studies that clearly elaborated the linkage of nutrients with the immune system as well as additionally with metabolic paradoxes. However, the other irrelevant research articles were excluded out because they did not come under the inclusion criteria of this research work. Additionally, only published articles were used as the primary source of information in this current paper while the information from other sources is not part of this study. To gather all the information the researcher took approximately two months for a search.

## 3. Results

### 3.1. Uric Acid Paradox

In living organisms and apes, purine metabolism provides uric acid as an end product (7). The process of purine catabolism is completely understood in vertebrates because 8-20 million years back during primate advancement the catalysis of proteins, uricase, and urate oxidase converted uric acid into allantoin which is discharged in pee in well-evolved organisms. After that, it was examined that lower vertebrates have proteins that further catalyzed allantoin into allantoic acid and glyoxylic acid that ultimately formed urea (8). Uric acid is a very important component because it has many benefits like it can significantly prevent cancer in humans, strongly

predicts cardiovascular ailment, hypertension, conditions related to oxidative pressure as well as rapidly increasing body weight. However, in living organisms, there is a need to properly adapt the optimum level of uric acid in blood plasma because its elevated concentration in the blood leads to hyperuricemia and gout (9). Moreover, it was also observed that the oxidation of uric acid had a great impact on normal cardiac activity and thus leads to the prognosis of various types of cardiovascular disorders (7). Apart from the formation of superoxides from uric acid which has an adverse impact on the human body, uric acid exhibits a strong connection with a few oxidants that have a defensive role in specific conditions (10). In hydrophilic conditions, molecules of uric acids lost their potential to prevent cancer in a cell. Additionally, the reaction of uric acid molecules with different types of oxidants might form various radicals, and a high concentration of radicals leads to oxidative stress which is harmful to the cell. All of these contemplations taken together completely clarified the cancer inhibitory role of the uric acid agent paradox in hydrophilic conditions (11).

### 3.2. Tgf-Beta Paradox

TGF-beta ( $\beta$ ) has a significant role in various mechanisms of the body including wound healing, organogenesis, tumor production, and development of resistance against different diseases as well as in embryonic developmental processes. However, researchers had found another remarkable role of tgf- $\beta$  in malignancy because they potentially promote the abnormal differentiation of tissues while obstructing growth in benign cells, and this phenomenon is known as the tgf- $\beta$  paradox but the actual mechanism of this tgf- $\beta$  paradox is not known (12). Despite various experimentations and reports the puzzle of this paradox is still under question and needs more precise and deep knowledge to answer this secret. Initially, it was seen that differential Erk was activated through tgf stimulation of malignant cells and that Erk was considered as the main point of tgf

paradox between tumor and benign cells. All of these critical events that occur due to tgf- $\beta$  set the baseline for the “vicious cycle of TGF- $\beta$  signaling”. For the prediction of the aggressive metastatic stage, there are three types of tgf biomarkers are available known as Tgf $\beta$ 1, Tgf- $\beta$ 2, and Tgf- $\beta$ 3, and their biogenic potency is further regulated by another set of specified receptors termed as TBRI and TBRII. After that these receptors work through different canonical (Smad) and non-canonical (pp2a-b56 $\alpha$ ) pathways to up-regulate the process of tumor progression and metastasis (13). These three occasions somehow clarify the puzzle of the tgf- $\beta$  paradox but it required further exploration (14). Proper understanding of tgf- $\beta$  paradox mechanism will assist researchers and oncologists in finding out the sluggish reasons behind malignancy and abnormal cell growth as well as it will help to design novel strategies to control this ailment. Initially, the term tgf- $\beta$  paradox did not properly depict that tgf- $\beta$  receptors were involved in hindering the cell cycle in benign cells while activated in cancerous cells. But now it has been cleared that cells could efficiently exhibit abnormal multiplication even in low concentrations of tgf- $\beta$  (15). Another report suggested that besides malignancy, cells could be hindered by tgf- $\beta$ , particularly in the initial stages of cancer if there is an adequate amount of TBRS receptors present (16).

### 3.3. IL-6 Paradox

Insulin resistance is the major driving factor behind the onset of type 2 diabetes also known as diabetes mellitus which is further involved in low-grade chronic inflammation and also in increasing the level of cytokines in the blood. It has been indicated that in peripheral tissues during chronic diseases insulin resistance was mediated by a high level of circulating IL-6 which is the best biomarker for identifying the process of insulin resistance (17). During exercise or hard physical activities, the endogenous level of IL-6 significantly raised which is good for insulin sensitivity. Both these functions

prompted the query that how high IL-6 level regulates insulin resistance in the body while it also possesses a role in insulin sensitivity. Thus it is very important to understand both functions of this cytokine to develop better treatment regimes (18). Previous studies have stated that due the AMP-kinase pathway is activated due to leptin resistance and adiponectin in the body which indicated that there is a close association among IL-6 and leptin flagging pathways that are more specifically linked with insulin resistance in the body. All of these processes are further involved in the activation of stat3 and soc3 cycles (19). Under normal physiological conditions, the level of circulatory IL-6 is usually higher but after sometimes the level of this cytokine drops down. However, this transient elevation of circulatory IL-6 did not cause activation of socs3 yet this transient change significantly enhance the process of insulin sensitivity (20).

#### **3.4. Exercise Paradox**

Information regarding total calories intake and consumption is very important for the maintenance of human health as well as for daily activities. Physical exercise is most important because it helps to consume excess calories efficiently that aid in controlling the weight of an individual (21). Moreover physical activities on a regular basis help in forestalling atherothrombotic sicknesses. However, the exercise paradox might happen due to improper testing of thrombotic and thrombolytic statuses in the cell at a particular time.

In order to observe thrombotic and thrombolytic status, a blood test was conducted. A shear-incited thrombosis/endogenous fibrinolysis test was performed with a non-anti-coagulated blood sample before and after any physical activity of humans which provides information regarding thrombotic condition (22). Therefore this delicate and physiologically applicable test gives precise information about the previously mentioned exercise paradox. However, analysts have sullenly reported that the values of tests do not alter with how much

physical activity or exercise an individual does daily. Apart from weight reduction exercise helps in the proper digestion of high-calorie food because the improper digestion of food will restrict the reduction of weight. In order to inhibit the prognosis of atherothrombotic disorders devised the utilization of an antithrombotic diet which will give beneficial results in this regard. Most importantly individuals having serious dynamics in their everyday lives consumed a similar number of calories regularly as compared to those who have reasonably dynamic living styles (22). However, in terms of exercise, the most important point which matters a lot is its sustenance as compared to how much you do physical activity. Thus exercise is a basic but beneficial and profitable activity from a metabolic point of view because it enhances the rate of metabolism that helps in cutting extra fat deposition of the body. Eating nutritionally rich and healthy food that does not contain a high amount of calories could energize the body according to its need without permitting it to deposit extra fat which is harmful (23). As well as from the plate of mixed green vegetables rather than smoothies and nuts could provide more nourishment to your body. Thus the fact is that cerebrum could fantastically scan for nourishment while our bodies were intended to voraciously accumulate fats regardless of caloric expense (24).

#### **3.5. Calcium Paradox**

In 1966 scientist Zimmerman and Hülsmann (25) first-time stated information and detailed description about the calcium paradox. At that time, studies related to the calcium paradox were a hot topic among the scientific community, and researchers were enthusiastic to know about the effect of calcium particles on heart muscles. Later it was indicated that extra deposition of calcium ions in heart muscles causes the onset of various harmful disorders like ischemia-reperfusion of myocardium, abnormal electrical and physical activities as well as contracture development (26). Even though all the essential components do not disrupt the normal

functioning of cell-only few components are responsible for cell injury as well as in severe cases their disruption leads to cell death. However, in the case of the calcium paradox which possesses intricate intracellular associations with different types of cells, it has been found that this calcium paradox is a basic key factor behind the discontinuity in the normal functioning of a cell which leads to major cell injury (27). Through the calcium paradox, one can easily examine the biochemical, morphological, and electrophysiological reasons behind the myocardial injuries that happen due to excess restoration of extracellular calcium ions. Additionally, scientists stated that there is a major discrepancy in cellular injury processes caused by ischemia-reperfusion as well as through calcium paradox. Increased grouping of calcium ions, high concentration of calcium channel blocker, hyponatremia which is low sodium level in the blood, and hypothermic condition which is associated with a lower-body temperature that 35 degrees Celsius are major hallmarks behind the progression of calcium paradox and ischemia-reperfusion. In these situations due to  $Ca^{+2}$ , free superfusion cell injuries become obvious and nothing can stop this critical situation (28). In the era of 1980s deep and detailed studies were conducted regarding calcium ion restoration and its impact on heart cells. After that, they argued that expansion of calcium particles in heart cells are major driving factors that cause lysis of heart tissues by creating pores in tissues which ultimately leads toward the onset of severe heart diseases (29). Hypocalcemia cardioplegia is a viable phenomenon in order to improve heart arrest. Moreover, various types of substances are available that have the ability to obstruct unwanted reactions due to calcium ion restoration thus can forestall ventricular brokenness after a cardiopulmonary detour (30). A few speculations are present that clarify the calcium paradox to some extent, studies explained calcium

paradox as greater penetrability of calcium ions in the sarcolemma, glycocalyx which cause detachment of intercalated discs due to which cell injury and destruction of myocytes film that causes expulsion of cells. Still, there are gaps because the entire mechanism of the calcium paradox is unclear and needs further information. Apart from these the insufficient synthesis and consumption of calcium can cause harmful effects to the human body which are further associated with consumption of caffeine and can cause mechanical strain on the heart (31).

### 3.6. Lanolin Paradox

Lanolin is also known as fleece yolk, fleece wax, or fleece oil. It is a wax emitted by the sebaceous organs of the organisms that have fleece. People utilize lanolin for different purposes which are taken from residential sheep. Excessive bleeding of the sheep must be done in order to get fleece yolk, fleece oil and fleece was from them (32). The skin of sheep secretes lanolin oil which has various applications. However, lanolin oil from sheep does not possess any traces of triglycerides in its structure like human sebum. Sometimes lanolin is considered as "fleece fat" but this term should not be a delusion because it does not contain triglyceride which is known as fat. Additionally, due to molding properties, this substance has broad application in all beautifying agents like skin and hair-related products (33). Lanolin oil that is also termed as emollient can be removed from the fleece of sheep with the help of a rotatory machine that isolates the oil from different synthetic concoctions and flotsam and jetsam. Moreover emollient is best to cure skin-related disorders because it possesses extraordinary hydrating properties that can soothe dry, flaky skin (34). Numerous items that contain lanolin oil additionally contain humectants fixings like aloe, nectar, or glycerin (35). Apart from the positive sides, there are certain confusing aspects related to the utilization of lanolin which is known as 'lanolin paradoxes' in relationship with the 'paraben paradoxes'. Lanolin is prescribed to those patients who suffer from severe dermatological issues due to dry and acne skin they feel

discomfort and unpleasant vibes so dermatitis suggests them to use lanolin containing beauty care products on regular basis (36).

### 3.7. Glutamine Paradox

Glutamic acid is an alpha-amino acid that is utilized for the biosynthesis of proteins in all living organisms. Glutamic acid is trivial in human beings that mean the body can homogenize this amino acid completely and efficiently. It is a corrosive amino acid that is utilized in the framing of protein and living organism glutamic acid transforms in glutamate which does not harm the body as well as it in vertebrates it is also present in sensory system because it helps in transferring information from the brain towards different parts of the body as well as receive information from the body and convey to the brain (37). It has been investigated that it might have roles in memory formation and the learning process as well (38). Inside the body, the original glutamine compound is converted into glutamate through the c-myc cycle which is then further catabolized in the TCA cycle (39). It was observed that overexpression of *gs*, as well as a higher concentration of glutamine, regulates the process of nucleotide combination and amino corrosive vehicle. Due to this myc prompts the union of glutamine molecules that further develop a strong link in the DNA methylation process that ultimately leads to the development of myc mediated glutamine tumor formation (40). After that, the abnormal growth of cells revamps the metabolic projects including unusual glutamine break down that aid in the development, expansion, and endurance of malignant tumors. Among them, some malignant cell lines exhibited increased glutamine uptake and were fueled by catabolism that occurred through the TCA cycle (41). Moreover, being a supplemental substance this glutamic acid is a key tool for transportation of different types of amino acids in the body that detoxify extra amounts of glutamate resulting in tumor formation as well as it is also used as a nitrogen source in the body for the union of various types of cells (42).

### 3.8. Paraben Paradox

A variety of perplexing marvels associated with clinical, immunological, and restorative dermatology have been depicted. While some of them can be rationally explained, the causes of others must be conjectured. Foundation information on such paradoxes may be useful to clinicians at any point in their clinical practice (43). Diagnosing dermatological conditions has always piqued my interest. Several insignificant conditions present with clearly comparable morphology and frequently show testing to the undeveloped eyes. Even, the presence of a few muddled equivalent words for evidently common conditions doesn't improve the current situation. Additionally, a few clinical, immunological, and remedial dermatology paradoxes and misunderstandings have been depicted. Despite the obvious, a basic understanding of such paradoxes could be useful in clinical practice when such situations arise (44).

The "paraben paradox" is a notable marvel in hypersensitive contact dermatitis. P-hydroxybenzoic esters (parabens) are corrosive p-hydroxybenzoic esters (45). Prescriptions, beauty care products, glue swaths, ultrasound gels, dentifrices, suppositories, and staples are all common uses for methyl, ethyl, propyl, and butyl p-hydroxybenzoate. It portrayed two paradoxical wonders identified with paraben; one of them is paraben containing toiletries that are basic reasons for contact sensitivity frequently produces bogus negative outcomes while fixing on the back. Many people who are unfavorably susceptible to parabens (fix test positive) can continue to use beauty care products containing them on normal skin without developing dermatitis, but they react to such topical prescriptions when applied to damaged skin (e.g., venous ulcer). Fisher attributed these accomplishments to the insufficiently low centralization of parabens in cosmetics that fail to deliver contact sensitivity on normal skin, as well as the way that fixes testing is also extended to

ordinary skin. Fisher proposed the "esterase" and "microbial metabolite" terminologies to explain the paraben paradox (46). The esterases in subcutaneous tissue hydrolyze the least responsive long-chain parabens (butylparaben), whereas the esterases in the epidermis use the highly responsive short-chain parabens (methyl and propylparaben). Thus, a weakened epidermis is linked to improved digestion as well as increased entry of short-chain, highly responsive parabens into the subcutaneous tissue, resulting in an unfavorably susceptible response. According to the microbial metabolite theory, repeated use of paraben containing topical arrangements causes paraben-safe microbial strains to multiply (47). Parabens are hydrolyzed by these creatures into hydroxyl benzoic corrosive, which causes or highlights sharpening.

### 3.9. Vitamin C Paradox

Ascorbic acid has a variety of cancer-prevention properties, but it can also have competent oxidant effects in vitro, owing to its association with different metal particles. So far, it's unclear whether these master oxidant effects have any organic significance: a portion of the available information has been condensed. Nutrient c, also known as ascorbic corrosive, is a small sugar particle discovered in the 1920s by Albert von Szent-Gyorgyi, who discovered that it could prevent and cure scurvy (48). Scurvy is a threatening condition that affects people who do not consume natural products or vegetables for long periods. Kazimierz funk had compiled a list of nourishing variables, known as nutrients, whose deficiencies cause severe maladies in people ten years prior. Funk used the letter "c" in his list to designate an unidentified factor that is known to prevent scurvy. Later, Szent-Gyorgyi and Haworth created an artificial distinction between "C" and "ascorbic corrosive," and named it as such because of ascorbic means "against scurvy" (49). Over the next century, what we now call vitamin C became one of the most well-known medications in human history.

Aside from causing scurvy in humans, nutrient C is also essential for various species. Because neither animals nor plants can survive without vitamin C, it's amazing that some organisms have lost the ability to deliver it over time (50). In light of recent research that revealed that nutrient C controls a key pressure-activated translation factor called hypoxia-inducible factor 1 (hif1), a protein that, when activated directs the outflow of many pressure-related qualities, another theory has been proposed (51). The activation of hif1 occurs frequently when there is insufficient oxygen or nutrient C. As a result, it was proposed that living beings that have lost nutrient C biosynthesis are in a better position, they can finely control hif1 actuation based on nutrient C intake through the diet. The hif1 translation factor is less dynamic when nutrient C supply is adequate than when nutrient C supply is insufficient (52). At the end of the day, the lack of nutrient C biosynthesis allows our bodies to determine our dietary status and, as a result, set the proper hif1 articulation standard. It has the appearance of a delicate titration framework. Nutrient C, which was first identified as a factor in preventing scurvy disease, has since become well known for its anti-cancerous properties. Nutrient C is a significant co-substrate of a wide range of compounds, and it regulates quality articulation by associating with important interpretation factors, among other things (53).

### 3.10. Iodine Paradox

Iodine deficiency is a major global public health problem. "All nourishment grade salt, used in family and nourishment handling, should be invigorated with iodine as a safe and compelling technique for the avoidance and control of iodine inadequacy issue in populaces living in stable and crisis settings", according to the World Health Organization (WHO) (54). All-inclusive salt iodization (usi) was implemented in more than 120 countries after the WHO and the United Nations Children's Fund (UNICEF) recommended it in 1993. Simultaneously, monitoring iodine fixation in salt is advised to avoid excessive iodine intake (55). Nonetheless, rather than surveying iodine consumption,

estimation of urinary iodine concentration (UIC) or urinary iodine discharge per day (UIE) in a population is suggested as a proxy for late iodine admission because "urinary iodine is a widely recognized, cost-effective, and easily accessible pointer for iodine status" (56).

In some weak individuals, excessive iodine intake is associated with hyperthyroidism or hypothyroidism. Iodine-activated hyperthyroidism (iih) has been explained as an iodine supplementation reaction. "Jod-Basedow wonder" is another name for it (57). iih is most likely to occur in people who have thyroid nodular changes or in populations where iodine consumption is linked to a long-term iodine deficiency. Delange, De Benoist (58) depicted iih in two African countries that had recently experienced severe iodine deficiency and had recently been given iodized salt, but with poor monitoring. In contrast, only a few papers have shown iih in iodine-abundant countries around the world. After the organization of a high portion of iodine in iodine-adequate zones, iih was first discovered in people living in Boston (59). Hypothyroidism is the inverse reaction to high iodine levels. Overall, hyper- and hypothyroidism, goiter, and knob were all investigated, as well as admissions to an overabundance of iodine. Although it reduces goiter, constant exposure to excessive iodine from water or insufficiently monitored salt is a risk factor for hypothyroidism in free-living populations. Future all-around structured observational investigations, particularly those detailing balanced outcomes, are required due to the low quality and the limited number of included examinations. Thyroid antibodies, as well as sub-bunch investigations, are required (60).

### 3.11. IGF-1 Paradox

Aging is a continuous and gradual process that is characterized as a decrease in natural physiological processes in the body that are essential for the fertility and survival of human beings. In mature humans, the

phenotype is amazingly heterogeneous and can be portrayed as a mind-blowing mosaic pattern that takes place as a consequence of various types of stochastic and natural occasions, variation in hereditary material, and epigenetic alterations, all of these events occur lifetime (61). The phenomenon of early aging could be restricted by utilizing the hereditary and hormonal framework from normal predecessors (62). In different organisms like flies, nematodes, and mammals, one pathway found that has been embroiled for maturation is the insulin/insulin-like development factor (IGF-1) flagging, which is further linked with numerous other components that are essential for digestion, development, and nourishment. It was observed that interruption of the insulin/IGF-1 receptor in nematodes and flies enhanced the life expectancy (63). In higher vertebrates, insulin/IGF-1 receptors are present in numerous organs however their capacities are inverse in a different event because they are situated in the focal sensory system or the fringes however in lower vertebrates the insulin/IGF-1 receptors chiefly flag in the sensory system. Besides other species, mammals have unique, defined, and specified receptors for insulin and IGF-1 involved in particular pathways. Previous studies and research works proposed that a low level of IGF-1 receptors during early stages will significantly tweak life span in numerous species (64). Thus paradoxical results followed the abatement of insulin and potential IGF-1 receptors pathway in spineless organisms as well as in warm-blooded animals in order to minimize the process of early aging. That's why researchers are considering all of the above downstream processes to implement insulin and IGF-1 motioning in human in order to increase their life span. Additionally the central focusing point among all strategies to control early aging is endocrine profiling as well as calorie control diet (65). Among all the procedures balancedgh/igf-1/insulin frameworkproved beneficial in order to increase life span of individuals (66) (Table 1).



**Table 1.** The main metabolic paradoxes and their impact on metabolism

Metabolic Paradox	Interaction with Immune System	References
Uric acid paradox	Prevent cancer in humans, reduce obesity, increase level in blood leads to hyperuricemia, reduce hypertension	(67)
Tgf beta paradox	Induce organogenesis, involves in wound healing, resistance against different diseases, tumor production	(68), (69)
Il6 paradox	Onset of type 2 diabetes, low grade chronic inflammation, high level of cytokines, regulates insulin resistance	(20), (70)
Exercise paradox	forestal atherothrombotic sicknesses, weight reduction, proper digestion of high calorie food, enhances the rate of metabolism	(24), (25)
Calcium paradox	Ischemia-reperfusion of myocardium, cell injury, hyponatremia & hypothermic condition, cause mechanical strain on the heart	(71), (72)
Lanolin paradox	Cure skin related disorders	(73)
Glutamine paradox	Roles in learning process and memory formation, detoxify extra amino acids from the body	(76)
Paraben paradox	Use in beauty care products	(46)
Vitamin c paradox	Prevent scurvy disease, anti-cancerous properties	(75)
Iodine paradox	hyperthyroidism or hypothyroidism, goiter	(76)
Igfl paradox	Enhance the life expectancy, improve digestive system, minimize early aging	(66)

#### 4. Conclusions

The information regarding complacency and survival of individuals from different nations exhibited various astonishing and unseen realities as well as paradoxical associations. The complacency status of individuals from a specific nation is the result of different factors which can't be changed every day. French paradox is the most established case that depicted clear-cut complexity between "undesirable" sustenance and mortality due to a few cardiovascular disorders. However, the people of Switzerland consume a high amount of fats, milk, and dairy products but the mortality rate due to cardiac disorder of Swiss people is low. In the USA the concomitant increase of body weight and the reduced cardiovascular mortality rate were observed. Studies indicated that the future of Albania is significantly higher as compared to other central European nations and in the Balkan area regardless of the fact that Albania remained the most unfortunate European nation. Evaluation of these facts and paradoxical relations demonstrated the significance of the clinical consideration, control of factors that

cause cardiac disorders, and careful eating routine with low calories to avoid ailment in Cuba and Albania. The experiences of socialists from different central European nations recommended that high blood pressure and psychosocial factors had a significant impact on heart illnesses.

#### Authors' Contribution

Study concept and design: A. G.

Acquisition of data: S. P.

Analysis and interpretation of data: A. M.

Drafting of the manuscript: S. N.

Critical revision of the manuscript for important intellectual content: A. G.

Administrative, technical, and material support: A. G.

#### Conflict of Interest

The authors declare that they have no conflict of interest.

#### References

1. Titan SM, Bingham S, Welch A, Luben R, Oakes S, Day N, et al. Frequency of eating and concentrations of

- serum cholesterol in the Norfolk population of the European prospective investigation into cancer (EPIC-Norfolk): cross sectional study. *Br Med J*. 2001;323(7324):1286.
2. Alencar MK, Beam JR, McCormick JJ, White AC, Salgado RM, Kravitz LR, et al. Increased meal frequency attenuates fat-free mass losses and some markers of health status with a portion-controlled weight loss diet. *Nutr Res*. 2015;35(5):375-83.
  3. Jenkins DJ, Wolever TM, Vuksan V, Brighenti F, Cunnane SC, Rao AV, et al. Nibbling versus gorging: metabolic advantages of increased meal frequency. *N Engl J Med*. 1989;321(14):929-34.
  4. Nieuwenhuizen AG, van Schothorst EM. *Energy metabolism and diet*. Multidisciplinary Digital Publishing Institute; 2021.
  5. Cooney C, Daly E, McDonagh M, Ryan L. Evaluation of measured resting metabolic rate for dietary prescription in ageing adults with overweight and adiposity-based chronic disease. *Nutrients*. 2021;13(4):1229.
  6. Andersen RM, Fleming GV, Champney. Exploring a paradox: belief in a crisis and general satisfaction with medical care. *Milbank Mem Fund Q Health Soc*. 1982;329-54.
  7. Lin K-M, Lu C-L, Hung K-C, Wu P-C, Pan C-F, Wu C-J, et al. The paradoxical role of uric acid in osteoporosis. *Nutrients*. 2019;11(9):2111.
  8. Gersch C, Pali SP, Imaram W, Kim KM, Karumanchi SA, Angerhofer A, et al. Reactions of peroxynitrite with uric acid: formation of reactive intermediates, alkylated products and triuret, and in vivo production of triuret under conditions of oxidative stress. *Nucleosides*. 2009;28(2):118-49.
  9. Robinson KM, Morr e JT, Beckman JS. Triuret: a novel product of peroxynitrite-mediated oxidation of urate. *Arch Biochem*. 2004;423(1):213-7.
  10. Kaushal N, Vohora D, Jalali RK, Jha S. Review of the literature examining the association of serum uric acid with osteoporosis and mechanistic insights into its effect on bone metabolism. *Endocr metab immune disord drug targets*. 2019;19(3):259-73.
  11. Xu M, Su J, Hao J, Zhong N, Zhang Z, Cui R, et al. Positive association between serum uric acid and bone mineral density in Chinese type 2 diabetes mellitus stratified by gender and BMI. *J bone miner metab*. 2018;36(5):609-19.
  12. Zhang Q, Yu N, Lee C. Mysteries of TGF- $\beta$  paradox in benign and malignant cells. *Front Oncol*. 2014;4:94.
  13. Zhang Q, Yu N, Lee C. Vicious cycle of TGF- $\beta$  signaling in tumor progression and metastasis. *J Clin Exp Urol*. 2014;2(2):149.
  14. Yu N, Kozłowski JM, Park II, Chen L, Zhang Q, Xu D, et al. Overexpression of transforming growth factor  $\beta$ 1 in malignant prostate cells is partly caused by a runaway of TGF- $\beta$ 1 auto-induction mediated through a defective recruitment of protein phosphatase 2A by TGF- $\beta$  type I receptor. *Urology*. 2010;76(6):1519.
  15. Vega JL, Puebla C, V squez R, Far as M, Alarc n J, Pastor-Anglada M, et al. TGF- $\beta$ 1 inhibits expression and activity of hENT1 in a nitric oxide-dependent manner in human umbilical vein endothelium. *J Cardiovasc Res*. 2009;82(3):458-67.
  16. San Mart n R, Sobrevia L. Gestational diabetes and the adenosine/L-arginine/nitric oxide (ALANO) pathway in human umbilical vein endothelium. *Placenta*. 2006;27(1):1-10.
  17. Sarvas JL, Khaper N, Lees SJ. The IL-6 paradox: context dependent interplay of SOCS3 and AMPK. *Diabetes Metab J*. 2013.
  18. Steinberg GR, Smith AC, Van Denderen BJ, Chen Z, Murthy S, Campbell DJ, et al. AMP-activated protein kinase is not down-regulated in human skeletal muscle of obese females. *J Clin Endocrinol Metab*. 2004;89(9):4575-80.
  19. Chen MB, McAinch AJ, Macaulay SL, Castelli LA, O'Brien PE, Dixon JB, et al. Impaired activation of AMP-kinase and fatty acid oxidation by globular adiponectin in cultured human skeletal muscle of obese type 2 diabetics. *J Clin Endocrinol Metab*. 2005;90(6):3665-72.
  20. H jlund K. Metabolism and insulin signaling in common metabolic disorders and inherited insulin resistance. *Dan Med J*. 2014;61(7):B4890..
  21. Pontzer H. The Exercise Paradox.(Cover story). *Sci Am*. 2017;316(2):26-31.
  22. Ikarugi H, Yamamoto J, Ijiri Y, Iwasaki M, Murakami M, Matsuo O, et al. Evaluation of antithrombotic effect: importance of testing components and methodologies. *Drug Discov Ther*. 2015;9(4):258-66.

24. Yamamoto J, Inoue N, Otsui K, Ikarugi H, Shimizu M, Yamamoto S, et al. A point-of-care global thrombosis test measuring occlusion time and endogenous lysis time may indicate thrombotic status. *Future Science*; 2019.
25. Zimmerman A, Hülsmann W. Paradoxical influence of calcium ions on the permeability of the cell membranes of the isolated rat heart. *Nature*.1966;211(5049):646-7.
26. Oliveira MABd, Brandi AC, Santos CAd, Botelho PHH, Cortez JLL, Goissis G, et al. The calcium paradox-what should we have to fear? *Braz J Cardiovasc Surg*. 2014;29:249-54.
27. Calvi L, Pavlovic R, Panseri S, Giupponi L, Leoni V, Giorgi A. Quality traits of medical Cannabis sativa L. inflorescences and derived products based on comprehensive mass-spectrometry analytical investigation. *Recent Advances in Cannabinoid Research: IntechOpen*; 2018.
28. Kojima A, Kitagawa H, Omatsu-Kanbe M, Matsuura H, Nosaka SJBjop. Ca<sup>2+</sup> paradox injury mediated through TRPC channels in mouse ventricular myocytes. *Br J Pharmacol*. 2010;161(8):1734-50.
29. Huang J, Hove-Madsen L, Tibbits GFJAJoP-CP. Ontogeny of Ca<sup>2+</sup>-induced Ca<sup>2+</sup> release in rabbit ventricular myocytes. *J Physiol*. 2008;294(2):516-25.
30. Shin S-Y, Choo S-M, Woo S-H, Cho K-HJPPi. Cardiac systems biology and parameter sensitivity analysis: intracellular Ca<sup>2+</sup> regulatory mechanisms in mouse ventricular myocytes. *Protein J*. 2008;25-45.
31. Kim TH, Shin SY, Choo SM, Cho KHJBJHNT. Dynamical analysis of the calcium signaling pathway in cardiac myocytes based on logarithmic sensitivity analysis. *Biotech J*. 2008;3(5):639-47.
32. Wolf R. The lanolin paradox. *Clinics in dermatology. J Dermatol* 1996;192(3):198-202.
33. Matthieu L, Dockx P. Discrepancy in patch test results with wool wax alcohols and Amerchol® L-101. *Contact Derm*. 1997;36(3):150-1.
34. Knijp J, Bruynzeel DP, Rustemeyer T. Diagnosing lanolin contact allergy with lanolin alcohol and Amerchol L101. *Contact Derm*. 2019;80(5):298-303.
35. Miest RY, Yiannias JA, Chang Y-HH, Singh N. Diagnosis and prevalence of lanolin allergy. *Dermatitiss*. 2013;24(3):119-23.
36. Warshaw EM, Cook JW, Belsito DV, DeLeo VA, Fowler Jr JF, Maibach HI, et al. Positive patch-test reactions to mixed dialkyl thioureas: cross-sectional data from the North American Contact Dermatitis Group, 1994 to 2004. *Dermatitiss*. 2008;19(4):190-201.
37. Robert M, Schultz D, Wolf B, Cochran W, Schwartz A. Treatment of a neonate with propionic acidemia and severe hyperammonaemia by peritoneal dialysis. *Arch Dis Child*. 1979;54(12):962-5.
38. Ierardi-Curto L, Kaplan P, Saitta S, Mazur A, Berry G. The glutamine paradox in a neonate with propionic acidemia and severe hyperammonaemia. *J Inherit Metab Dis*. 2000;23(1):85.
39. Gortner L, Leupold D, Pohlandt F, Bartmann P. Peritoneal dialysis in the treatment of metabolic crises caused by inherited disorders of organic and amino acid metabolism. *Acta Pædiatrica*. 1989;78(5):706-11.
40. Celik M, Akdeniz O, Ozgun N. Efficacy of peritoneal dialysis in neonates presenting with hyperammonaemia due to urea cycle defects and organic acidemia. *Nephrol Dial*. 2019;24(3):330-5.
41. Arbeiter AK, Kranz B, Wingen A-M, Bonzel K-E, Dohna-Schwake C, Hanssler L, et al. Continuous venovenous haemodialysis (CVVHD) and continuous peritoneal dialysis (CPD) in the acute management of 21 children with inborn errors of metabolism. *Nephrol Dial*. 2010;25(4):1257-65.
42. Schaefer F, Straube E, Oh J, Mehls O, Mayatepek E. Association TA-ER. Dialysis in neonates with inborn errors of metabolism. *Nephrol Dial Transplant*. 1999;14(4):910-8.
43. Adya KA, Inamadar AC, Palit A. Paradoxes in dermatology. *Indian Dermatol Online J*. 2013;4(2):133.
44. Tu Y-K, Gunnell D, Gilthorpe MS. Simpson's Paradox, Lord's Paradox, and Suppression Effects are the same phenomenon—the reversal paradox. *Emerg Themes Epidemiology*. 2008;5(1):1-9.
45. Gilthorpe MS, Tu Y-K. Response to: Simpson's Paradox is suppression, but Lord's Paradox is neither: clarification of and correction to Tu, Gunnell, and Gilthorpe (2008) by Nickerson CA & Brown. *Emerg Themes Epidemiology*. 2020;17(1):1-2.
46. Ameringer S, Serlin RC, Ward S. Simpson's paradox and experimental research. *Nurs Res*. 2009;58(2):123.
47. Hernán MA, Clayton D, Keiding NJJjoe. The Simpson's paradox unraveled. *Int J Epidemiol*. 2011;40(3):780-5.
48. Halliwell B. Commentary: vitamin C: antioxidant or pro-oxidant in vivo? *Free Radic Res*. 1996;25(5):439-54.
49. Halliwell B, Murcia MA, Chirico S, Aruoma OI. Free radicals and antioxidants in food and in vivo: what

- they do and how they work. *Crit Rev Food Sci Nutr.* 1995;35(1-2):7-20.
50. St. Angelo AJ, Vercellotti J, Jacks T, Legendre M. Lipid oxidation in foods. *Crit Rev Food Sci Nutr.* 1996;36(3):175-224.
51. Sun Y-E, Wang W-D, Chen H-W, Li C. Autoxidation of unsaturated lipids in food emulsion. *Critical reviews in food science and nutrition.* 2011;51(5):453-66.
52. McClements DJ. Critical review of techniques and methodologies for characterization of emulsion stability. *Critical reviews in food science and nutrition.* 2007;47(7):611-49.
53. McClements DJ, Decker EA, Park Y, Weiss J. Structural design principles for delivery of bioactive components in nutraceuticals and functional foods. *Critical reviews in food science and nutrition.* 2009;49(6):577-606.
54. Zimmermann MB, Galetti V. Iodine intake as a risk factor for thyroid cancer: a comprehensive review of animal and human studies. *Thyroid Res.* 2015;8(1):1-21.
55. Katagiri R, Yuan X, Kobayashi S, Sasaki SJPo. Effect of excess iodine intake on thyroid diseases in different populations: A systematic review and meta-analyses including observational studies. *PloS one.* 2017;12(3): 0173722.
56. Du Y, Gao Y, Meng F, Liu S, Fan Z, Wu J, et al. Iodine deficiency and excess coexist in china and induce thyroid dysfunction and disease: a cross-sectional study. *PloS one.* 2014;9(11):111937.
57. Laurberg P, Jørgensen T, Perrild H, Ovesen L, Knudsen N, Pedersen IBI, et al. The Danish investigation on iodine intake and thyroid disease, DanThyr: status and perspectives. *Eur J Endocrinol.* 2006;155(2):219-28.
58. Delange F, De Benoist B, Alnwick DJT. Risks of iodine-induced hyperthyroidism after correction of iodine deficiency by iodized salt. *Thyroid.* 1999;9(6):545-56.
59. Laurberg P, Jørgensen T, Ovesen L, Rasmussen LB, Perrild H, Andersen S, et al. Iodine fortification of salt and thyroid disease in Denmark. *Ugeskr Laeger.* 2011;173(50):3264-70.
60. Rasmussen LB, Carlé A, Jørgensen T, Knudsen N, Laurberg P, Pedersen IB, et al. Iodine intake before and after mandatory iodization in Denmark: results from the Danish Investigation of Iodine Intake and Thyroid Diseases (DanThyr) study. *Br J Nutr.* 2008;100(1):166-73.
61. Rincon M, Muzumdar R, Atzmon G, Barzilai N. The paradox of the insulin/IGF-1 signaling pathway in longevity. *Mech Ageing Dev.* 2004;125(6):397-403.
62. Rincon M, Rudin E, Barzilai N. The insulin/IGF-1 signaling in mammals and its relevance to human longevity. *Exp Gerontol.* 2005;40(11):873-7.
63. Chistyakova O. Signaling pathway of insulin and insulin-like growth factor 1 (IGF-1) as a potential regulator of lifespan. *J Evol Biochem Physiol.* 2008;44(1):1-11.
64. Barbieri M, Bonafè M, Franceschi C, Paolisso G. Insulin/IGF-I-signaling pathway: an evolutionarily conserved mechanism of longevity from yeast to humans. *Am J Physiol- Endocrinol Metab.* 2003;285(5):1064-71.
65. Klötting N, Blüher M. Extended longevity and insulin signaling in adipose tissue. *Exp Gerontol.* 2005;40(11):878-83.
66. Picard F, Guarente L. Molecular links between aging and adipose tissue. *Int J Obes.* 2005;29(1):S36-S9.
67. Xu M, Su J, Hao J, Zhong N, Zhang Z, Cui R, et al. Positive association between serum uric acid and bone mineral density in Chinese type 2 diabetes mellitus stratified by gender and BMI. *J bone miner metab.* 2018;36(5):609-19.
68. San Martín R, Sobrevia LJP. Gestational diabetes and the adenosine/L-arginine/nitric oxide (ALANO) pathway in human umbilical vein endothelium. *Placenta.* 2006;27(1):1-10.
69. Vega JL, Puebla C, Vásquez R, Farías M, Alarcón J, Pastor-Anglada M, et al. TGF-β1 inhibits expression and activity of hENT1 in a nitric oxide-dependent manner in human umbilical vein endothelium. *J Cardiovas Res.* 2009;82(3):458-67.
70. Steinberg GR, Smith AC, Van Denderen BJ, Chen Z, Murthy S, Campbell DJ, et al. AMP-activated protein kinase is not down-regulated in human skeletal muscle of obese females. *J Clin Endocrinol Metab.* 2004;89(9):4575-80.
71. Kim TH, Shin SY, Choo SM, Cho KH. Dynamical analysis of the calcium signaling pathway in cardiac myocytes based on logarithmic sensitivity analysis. *Biotechnol J.* 2008;3(5):639-47.
72. Shin S-Y, Choo S-M, Woo S-H, Cho K-H. Cardiac systems biology and parameter sensitivity analysis: intracellular Ca<sup>2+</sup> regulatory mechanisms in mouse ventricular myocytes. *Adv Biochem Eng Biotechnol.* 2008;110:25-45.
73. Warshaw EM, Cook JW, Belsito DV, DeLeo VA, Fowler Jr JF, Maibach HI, et al. Positive patch-

- test reactions to mixed dialkyl thioureas: cross-sectional data from the North American Contact Dermatitis Group, 1994 to 2004. *Dermatitis*. 2008;19(4):190-201.
74. Ierardi-Curto L, Kaplan P, Saitta S, Mazur A, Berry GJJoimd. The glutamine paradox in a neonate with propionic acidaemia and severe hyperammonaemia. 2000;23(1):85.
75. McClements DJ, Decker EA, Park Y, Weiss J, nutrition. Structural design principles for delivery of bioactive components in nutraceuticals and functional foods. *Crit Rev Food Sci Nutr*. 2009;49(6):577-606.
76. Mcclements DJJCrifs, nutrition. Critical review of techniques and methodologies for characterization of emulsion stability. *Crit Rev Food Sci Nutr*. 2007;47(7):611-49.