THERMODYNAMIC ASPECTS OF HOMEOSTASIS

by
Cennet Yıldız

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APPROVED BY:

Prof. Dr. Mustafa Özilgen ……
(Thesis Supervisor)
(Yeditepe University)

Prof. Dr. Karsten Köhler ……
(Technical University of Munich)

Assoc. Prof. Dr. Ali Bahadır Olcay ……
(Yeditepe University)

Assoc. Prof. Dr. JALE Çatak ……
(İstanbul Sabahattin Zaim University)

Assist. Prof. Dr. Özge Tastan ……
(Yeditepe University)

DATE OF APPROVAL: ..../..../2023

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Name, Last name Cennet Yıldız

Signature …..…….……..

To my beloved family…

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ABSTRACT

THERMODYNAMIC ASPECT OF HOMEOSTASIS

Organisms sustain themselves at far-from thermodynamic equilibrium with their surroundings. The living organisms import energy and exergy, and export entropy to maintain constancy of their vital internal physiological components via homeostasis. Living systems generate entropy by reason of metabolic activity, the greatest amount of entropy is exported, whereas only a small amount of fraction accumulates. Accumulation shows itself as structural diminishing, considered an indication of ageing and measured as an information entropy. The entropic age theory implies that metabolic heat harms the living systems in the long term and leads to ageing. The term ‘human superorganism’ refers to the human host and the millions of microorganisms residing in and on the host. The gut microbiota plays a crucial role as an autonomous thermodynamic subsystem. It can generate and export entropy without age-related impairments. Thermodynamic analyses must be conducted to understand the entropy generated by the host and the gut. These analyses can help us quantify the entropy generation of both the host and the gut microbiota. This understanding is essential for understanding the role of the gut microbiota in the human superorganism. In recent years, research into the role of gut microbiota in human health and ageing has grown. This study has suggested that a large proportion of the metabolic entropy of the human superorganism, ranging from 12% to 59%, is generated by gut microbiota. This is exported with faeces without contributing to host ageing. This suggests that the gut microbiota could be a major factor in an individual's longevity. Although the gut microbiota has traditionally been studied for its nutritional benefits to the host, this newly hypothesised benefit to longevity needs to be studied further. This research could have implications for dietary and lifestyle interventions that increase lifespan expectations. The relationship between athletes' lifespan expectancies and the sports they are involved in can be explored through the entropic age concept. Previous nutrition studies have shown success with this method. To further investigate the relationship between athlete longevity and nutrition, athletes' caloric needs must be considered when designing diets for each athlete group. It is imperative to adhere to the latest guidelines when planning diets for athletes, as their caloric needs vary depending on the type of sport they participate in. Additionally, athletes must be given proper nutrition to perform at their peak and remain healthy and injury-free.

By doing so, athletes' lifespan expectancies can be improved and they can continue to pursue sports activities. This study suggests that athletes may extend their longevity significantly if they adjust their diet following retirement at 50. The predicted average longevity for male athletes was 56 years for cyclists, 66 years for weightlifters, 75 years for rugby players and 92 years for golfers. If they start consuming the retirement diet after 50 years of age, the life expectancy of the cyclists may increase for 7 years, and those of weightlifters, rugby players and golfers may increase for 22, 30 and 8 years, respectively. This demonstrates the impact of dietary change on life expectancy and suggests that athletes should not neglect their diet even after retirement. Athlete nutrition is crucial to sustaining the body's health status. Low-energy availability causes physiological dysfunction and a shorter lifespan. High-calorie intake and extreme caloric restriction diet decrease the longevity of athletes. Athletes should maintain energy balance in the body.

ÖZET

HOMOSTAZIN TERMODİNAMİK YÖNÜ

Organizmalar kendilerini çevreleriyle termodinamik dengeden uzak tutarlar. Canlı organizmalar enerji ve ekserji ithal eder ve homeostaz yoluyla hayati iç fizyolojik bileşenlerinin sabitliğini korumak için entropi ihraç eder. Canlı sistemler metabolik aktivite nedeniyle entropi üretirler, entropinin büyük bir kısmı dışarı verilirken, sadece küçük bir kısmı birikir. Birikim kendini yapısal bir azalma olarak gösterir, yaşlanmanın bir göstergesi olarak kabul edilir ve bir bilgi entropisi olarak ölçülür. Entropik yaş teorisi, metabolik ısının uzun vadede canlı sistemlere zarar verdiğini ve yaşlanmaya yol açtığını ima eder. "İnsan süper organizması" terimi, insan konakçıyı ve konakçının içinde ve üzerinde ikamet eden milyonlarca mikroorganizmayı ifade eder. Bağırsak mikrobiyotası otonom bir termodinamik alt sistem olarak çok önemli bir rol oynar. Yaşa bağlı bozulmalar olmadan entropi üretebilir ve dışa aktarabilir. Konak ve bağırsak tarafından üretilen entropiyi anlamak için termodinamik analizler yapılmalıdır. Bu analizler, hem konak hem de bağırsak mikrobiyotasının entropi oluşumunu ölçmemize yardımcı olabilir. Bu anlayış, bağırsak mikrobiyotasının insan süper organizmasındaki rolünü anlamak için gereklidir. Son yıllarda, bağırsak mikrobiyotasının insan sağlığı ve yaşlanma üzerindeki rolüne yönelik araştırmalar arttı. Bu çalışma insan süper organizmasının metabolik entropisinin büyük bir kısmının, %12 ila %59 arasında, bağırsak mikrobiyotası tarafından üretildiğini öne sürmektedir. Bu entropi, konakçı yaşlanmasına katkıda bulunmadan dışkı ile ihraç edilir. Bu olay, bağırsak mikrobiyotasının bir bireyin uzun ömürlülüğünde önemli bir faktör olabileceğini düşündürmektedir. Bağırsak mikrobiyotası, konakçıya sağladığı besinsel faydalar için geleneksel olarak çalışılmış olsa da, uzun ömürlülüğe yönelik bu yeni hipotez edilen faydanın daha fazla araştırılmasını gerektiriyor. Bu araştırma, yaşam süresi beklentilerini artıran diyet ve yaşam tarzı müdahaleleri için çıkarımlara sahip olabilir. Sporcuların yaşam beklentisi ile yaptıkları spor arasındaki ilişki, entropik yaş kavramı aracılığıyla incelenebilir. Önceki beslenme çalışmaları bu yöntemle başarı göstermiştir. Sporcu ömrü ile beslenme arasındaki ilişkiyi daha fazla araştırmak için, her sporcu grubu için diyetler tasarlanırken sporcuların kalori ihtiyaçları dikkate alınmalıdır. Kalorik ihtiyaçları katıldıkları spor türüne göre değiştiğinden, sporcular için diyet planlarken en son yönergelere uymak zorunludur. Ek olarak, sporculara en üst düzeyde performans göstermeleri, sağlıklı ve yaralanmadan

kalmaları için doğru beslenme verilmelidir. Bunu yaparak, sporcuların yaşam süresi beklentileri iyileştirilebilir ve spor aktivitelerini sürdürmeye devam edebilirler. Bu çalışma, sporcuların 50 yaşında emekli olduktan sonra diyetlerini düzenlerlerse yaşam sürelerini önemli ölçüde uzatabileceklerini öne sürmektedir. Erkek sporcular için tahmin edilen ortalama yaşam süresi bisikletçiler için 56, halterciler için 66, ragbi oyuncuları için 75 ve golfçüler için 92 idi. 50 yaşından sonra emeklilik diyetini tüketmeye başlarlarsa, bisikletçilerin yaşam beklentisi 7 yıl, haltercilerin, ragbi oyuncularının ve golfçülerin yaşam beklentisi sırasıyla 22, 30 ve 8 yıl uzayabilir. Bu, diyet değişikliğinin yaşam beklentisi üzerindeki etkisini göstermekte ve sporcuların emekli olduktan sonra bile diyetlerini ihmal etmemeleri gerektiğini önermektedir. Sporcu beslenmesi, vücudun sağlık durumunu sürdürmek için çok önemlidir. Düşük enerji mevcudiyeti fizyolojik işlev bozukluğuna ve daha kısa bir ömre neden olur. Yüksek kalori alımı ve aşırı kalori kısıtlaması diyeti sporcuların ömrünü azaltır. Sporcular vücuttaki enerji dengesini sağlamalıdır.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF SYMBOLS/ABBREVIATIONS

η	Efficiency
ADP	Adenosine diphosphate
ATP	Adenosine triphosphate
BMI	Body mass index
BMR	Basal metabolic rate
CON	Control diet
CR	Calorie restriction
LEA-LP	Caloric restriction diet with low protein content
LEA-HP	Caloric restriction diet with high protein content
DIT	Dietary-induced thermogenesis
EA	Energy availability
EE	Energy expenditure
EEE	Exercise energy expenditure
ek	Specific kinetic energy
ep	Specific potential energy
FFAR	Free fatty acids receptors
FM	Fat mass
FFM	Fat free mass
GPCRs	G protein-coupled receptors
h^-	Specific enthalpy at standart condition
h^-	Specific enthalpy at standart condition
h^{-*}	Specific enthalpy at 310 K
LEA	Low energy availability
NADH	Nicotinamide adenine dinucleotide
NEAT	Non-exercise activity thermogenesis
RMR	Resting metabolic rate
m	Mass
SCFS	Short-chain fatty acida
Sgen	Entropy generation rate
s	Specific entropy

T	Temperature
TEE	Total energy expenditure
Q	Heat
$\bar{Q}_{total}$	Total heat loss
u	Internal energy
W_{ATP}	Total work performance rate via ATP utilization

1. INTRODUCTION

When combined together, the hypothesis of Prigogine and Wiame [1], Schrödinger [2], Demirel and Sandler and Demirel [3–5] suggest that living organisms sustain themselves at a far-from-equilibrium state by importing energy, or exergy, and exporting entropy (Figure 1.1). Homeostatic regulations are imposed on these thermodynamic facts if the organism is equipped with them (Figure 1.2). A biological system attains temperature, pressure and ion concentration equilibrium with its environment only at death. While all the organisms live far from the equilibrium state, only the hibernating mammals may maintain their rate of metabolism at a minimum level near-equilibrium state, while keeping their body temperature slightly above that of the environment [6]. The organisms not only increase their entropy-exporting potential but also avoid entropy accumulation over time to sustain their presence and increase the exergy efficiency of the life processes [1,7]. If an organism cannot comply with these requirements it will accumulate entropy, cannot be able to maintain its structural order, eventually come to thermodynamic equilibrium with its environment and cease living. Homeostasis indicates the maintenance of constant physiological parameters within an organism. A summary of the hormone involved in energy homeostasis and the summary of the mechanisms involved in homeostasis are presented in Tables 1.1 and 1.2. Homeostasis is a whole-body process, involving the cooperation of several organs, especially the heart, lungs, liver, pancreas, kidneys, and brain coordinating the interactions between these organs, tissues and cells. Effective adaptation of the control engineering systems to internal and external disturbances inspired researchers to develop an analogy between them and homeostasis in living systems. The brain is the control centre for the body, monitoring the internal conditions and responding to any signs of deviation from the normal range. When the brain detects a deviation, it sends out signals along the motor nerve fibres to stimulate changes that will restore the internal conditions to the normal range. This response is the basis for homeostasis, the process by which the body maintains a stable internal environment [8]. The body is also continually monitoring levels of nutrients such as glucose, oxygen and electrolytes, and adjusting them to maintain homeostasis. When the body detects a decrease in a particular nutrient, it will take steps to increase the supply of that nutrient. For example, if the body detects a decrease in glucose, it will release hormones that stimulate the release of glucose from the liver into the bloodstream. A set point is a physiological value around which the normal range fluctuates. The nature of regulation of the physiological parameters

with feedback mechanisms in a living organism is more sophisticated than those of the engineering applications with non-living systems. We may state regulation of the total-body-sodium levels as a typical example; unlike with typical engineering applications, this system was claimed to be established by a series of steady states determined by several factors, including sodium intake (demonstrated in Table 1.1).

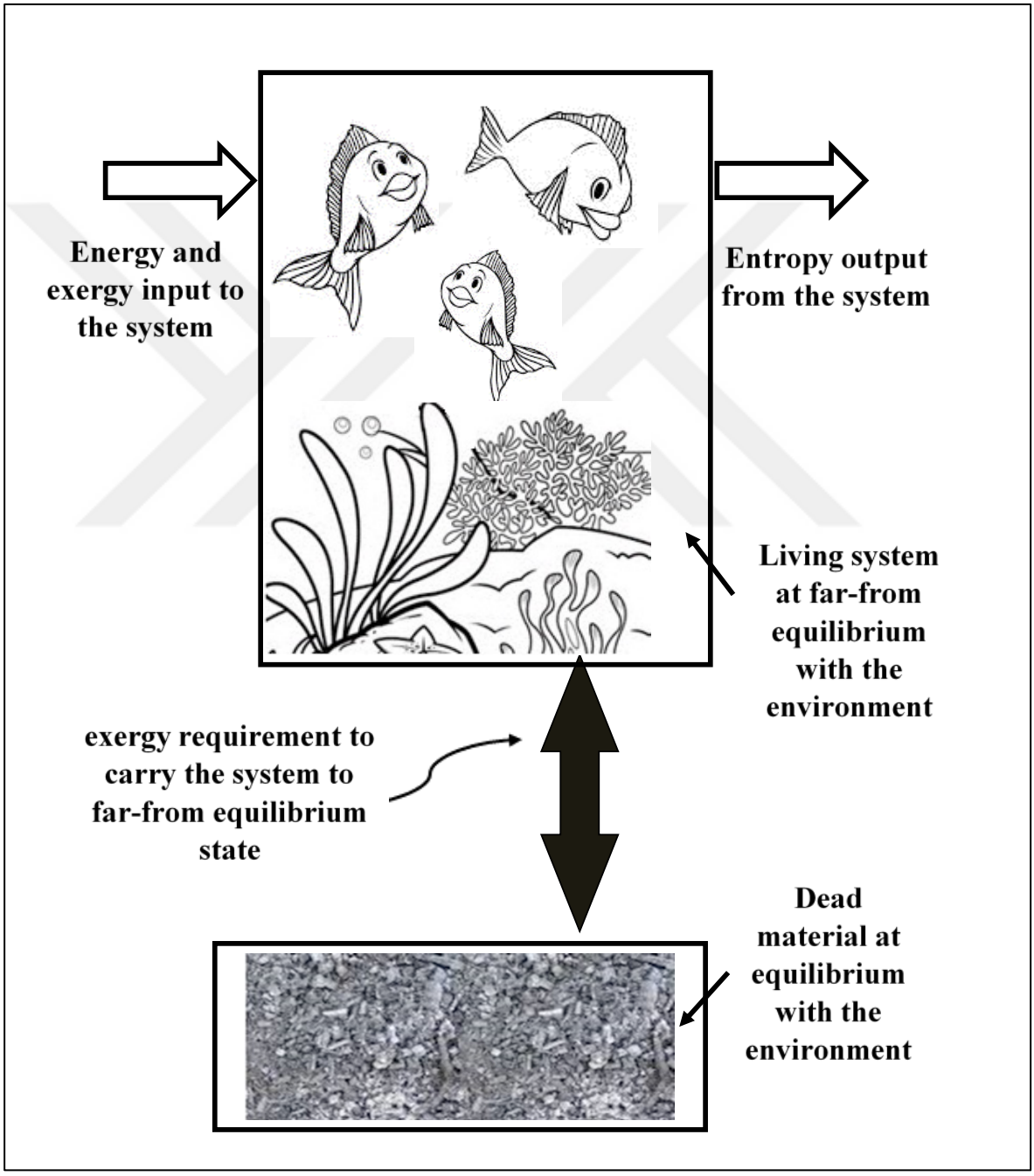

Figure 1.1. A living system thrives at far-from-equilibrium thermodynamic conditions, but it dies after coming to equilibrium with its environment

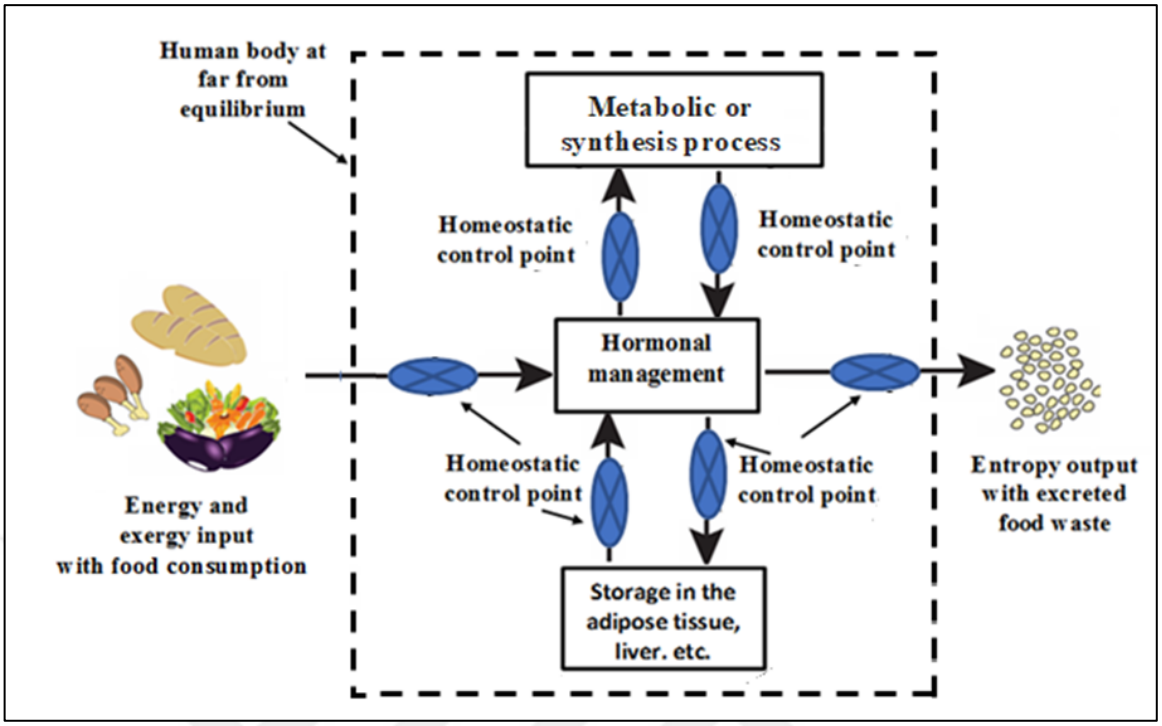

Figure 1.2. While the food provides the energy, or exergy, needed by the far-from-equilibrium living system, excreted materials, e.g., faeces, urine, CO2 etc. export the entropy. (There are also, ion, heat, etc. fluxes from the body. Homeostasis is tried to be maintained by controlling the mass, energy or exergy fluxes.)

The "*set point*", "*settling point*", and the "*dual intervention point models*" have been suggested to explain how the body controls its weight physiologically. According to the set point theory, body weight is regulated to a constant set point weight e.g., to the 'inherent body weight', by genetic, hormonal and metabolic control via a proportional feedback control system. The system appears to adjust the food intake or the energy expenditure in proportion to the difference between its current and the set point weights [9]. The set point of the system is maintained via the brain stem and hypothalamus. Then the homeostatic system adjusts the food or nutrient energy intake, energy expenditure and storage. Hormone involvement in homeostatic processes is described in Table 1.1. Set point theory does not explain how lifestyle and behaviour affect body weight regulation; therefore, scientists suggested the '*settling point*' theory, which states that diet and lifestyle establish the steady state of body weight. If energy intake or expenditure is regulated up or down in proportion to the body fat stores, the body weight comes to a natural balance. There is no '*set point*' for the body weight in this theory, but the system settles to an unregulated level. If adipose tissue

expands due to an increase in energy intake, energy expenditure increases to offset it [10–13].

Table 1.1. Summary of the hormone involved in energy, or exergy, homeostasis (adapted from [14–17]).

Hormone	Action
Ghrelin	Stimulates appetite, raises adiposity. Produced mostly in the stomach and in smaller extent in the brain. Most of its receptors are in the hypothalamus.
Leptin	Informs brain about the body fat mass. Produced primarily by the adipose tissue also in small amounts in the placenta and stomach. Signals decrease in the food intake and increase in energy expenditure to keep the size of the body fat stores unchanged
Glucagon and insulin	Secreted from the pancreas. When blood glucose level increases, insulin is secreted to signal transport of glucose into the muscles to suppress gluconeogenesis. If blood glucose level decreases, glucagon is secreted to stimulate liver for increasing hepatic glucose production to rise blood glucose level
Glucagon	Produced by the pancreas, promotes glucose breakdown in the liver, modulates lipid metabolism by activating lipolysis and inhibiting lipid synthesis, improves cardiac output, inhibits gastric motility and leads to body weight loss
Cholecystokinin	Cholecystokinin is released from the gastrointestinal tract in response to presence of fat and proteins in the digested food. It then gets into blood circulation and inhibits neurons in the satiety center in the hypothalamus. Thus, cholecystokinin provides a peripheral hormonal control on the mass input. If the level of cholecystokinin decreases in the plasma, hunger feeling increases and satiation decreases
Glucagon like peptides	Glucagon like peptide 1 is released in the intestines in response to meal intake. Decreased secretion of glucagon like peptide 1 may contribute to the development of obesity and exaggerated

	secretion may be responsible for after eating reactive hypoglycemia
Peptide YY	Produced by the small intestine and released into bloodstream after eating to tell the brain that the person is full. Fat is the most effective nutrient in secreting peptide YY. It has numerous roles such as narrowing of the blood vessels or inhibition of gastrointestinal motility
Pancreatic polypeptide	Pancreatic polypeptide Synthesized in the pancreas and gastrointestinal tract, increases in the plasma in parallel with the calorie intake. Reduces the food intake and prevents the body weight gain
Glucose dependent insulinotropic peptide	Produced by the small intestine in response to eating. Secretion depends on the type of the meal, fat and carbohydrates consumed. Encourages the release of insulin into the bloodstream to control the blood sugar levels. Its level in the blood increases with high-fat diet
Adiponectin	Increases glucose intake and fat oxidation in muscles and decreases fatty acid intake and glucose production in the liver, and insulin resistance. Adiponectin levels change in contrast with body weight, body fat mass and insulin levels
Oxyntomodulin	Synthesized from the gut in the postprandial state, reduces food intake, increases energy expenditure and causes body weight loss. Increases secretion of insulin from the pancreas and reduces gastric emptying
Vasopressin	Synthesized in the hypothalamus, is synthesized in the hypothalamus, plays a key role in maintaining osmolality [the concentration of dissolved particles, such as salts] in water in the body
Parathyroid and calcitonin hormones	Regulate calcium and vitamin D homeostasis
Aldosterone	Secreted by the adrenal glands and regulate salt, including potassium, and water homeostasis

Hepcidin	A small peptide hormone secreted in the liver, acts an important role in the regulation of iron homeostasis
Renin–angiotensin–aldosterone hormone system	A major hormonal cascade involving in the regulation of sodium homeostasis, fluid balance and blood pressure

The "*gene-by-environment*" interactions and their metabolic adaptations are addressed neither by the set point nor by settling point theories. Hence, an alternative concept "*dual intervention model*" is proposed. According to this model, the change in body weight depends on physiological, dietary, psychological and social factors and lifestyle changes. In this model, there are genetically controlled upper and lower intervention points, where active physiological regulation is implemented [10–12,18]. Between these intervention points, there is only a weak or no physiological regulation is done. The upper intervention point changes in a response to predation risk and the lower intervention point changes in response to starvation. These two-intervention points are adjusted independently. The difference between the upper and the lower intervention points may be extremely wide and its width may vary significantly between individuals. If body fatness decreases below the lower intervention point, the physiological mechanism stimulates energy or food intake in order to restore adipose tissue back to the previous level. However, when fatness rises excessively, similar physiological compensatory mechanisms are initiated to reduce energy intake. A two-intervention-point chart has been suggested by Özilgen [19] to keep the body mass index within approvable limits to assure healthy ageing.

Hormone involvement in mass, energy and exergy homeostasis is presented in Table 1.1 and its schematic drawing is presented in Figure 1.2. Communication between the brain and the tissues and the organs about satiety is achieved via neural circuits [20]. The neural circuits in the body integrate external and internal stimuli in the management of the energy balance to enact appropriate and consequential metabolic and behavioural responses. There are also claims that the gut microbiota involves in energy homeostasis with the contribution of the metabolites produced by the gut microbiome-derived metabolites [21]. The regulation of postprandial glycaemia is controlled by energy homeostasis. Glucose is the major energy source of the brain, red blood cells and most of the other tissues. Blood glucose levels of the mammalians are maintained mostly between 4.5 and 5.5 mmol/L. However, after ingesting

a carbohydrate-containing food, this range may increase to 6.5 and 7.2 mmol/L and may decrease to 3.3-3.9 mmol/L in starvation [22]. Blood glucose regulation is achieved via a highly sophisticated network of diverse hormones and neuropeptides with a concerted contribution of the brain, pancreas, liver and intestines apart from the adipose and muscle tissues (Tables 1.1 and 1.2). If carbohydrates reach more than the required level, the liver may transform glucose into glycogen and lipids, which are then may be used as metabolic fuels in case of starvation [23], as explained in Figure 1.2.

Undesired substances, such as toxic ions, are expelled and the desired mass, e.g., amino acids, is retained via mass homeostasis. Renal functions by employing glomerular filtration, tubular reabsorption and secretion mechanisms are of vital importance to maintaining fluid and electrolyte (ion) balance. Some of the filtrated substances (such as glucose and amino acids) are completely reabsorbed, and several ions (such as sodium, chloride, potassium and calcium) are reabsorbed to a great extent. Some other molecules, such as creatinine, are not reabsorbed and excreted into the urine after filtration and reabsorption processes [24]. In the aftermath of an overnight fast, 75-80% of the circulated glucose is secreted by the liver, while the remaining 20% is secreted by the kidneys [25]. Carbohydrate absorption is a major factor in glucose regulation in the body. After a meal is consumed, carbohydrates are broken down and absorbed into the bloodstream. This triggers glucagon and insulin secretion from the pancreas. These are two hormones that act together to regulate glucose metabolism in the liver and peripheral tissues. In this way, postprandial glucose levels, which measure the amount of glucose in the body after a meal, are determined. This process of carbohydrate absorption and hormone secretion is essential for maintaining healthy glucose levels in the body [26]. Following meal digestion, the body utilizes digested glucose in several ways. About 45% of glucose is transformed into glycogen in the liver, 30% is taken up by skeletal muscles, and the remaining is converted into glycogen. Of the glucose utilized, 15% is allocated to the brain, 5% to adipose tissue, and 10% to the kidneys. This is a process vital to the body's energy balance and metabolic functioning [23]. In times of limited food availability, adequate sleep is essential for maintaining homeostasis and regulating body weight. When sleep is insufficient, it leads to a disruption in the neuroendocrine system which impacts metabolic and behavioural functions. This can cause an increase in the hunger hormone ghrelin and a decrease in the satiety hormone leptin. This results in increased food intake and body weight increase. If individuals cannot get enough sleep, it can have serious

implications for their health and lead to an increased risk of obesity and other metabolic diseases. Therefore, it is essential to ensure that people get adequate sleep, especially in times of limited food availability. This is to maintain a healthy body weight [27].

Table 1.2. Summary of the mechanisms of ion balance, pH, glucose and protein recovery homeostasis [14].

Homeostatic process	How it is achieved
Regulation of the ion balance	Regulation of the ion balance is accomplished via a combination of filtration, tubular secretion and reabsorption in the kidneys. Transferrin receptors, located in the bone marrow and plasma membrane play major role in transferring and recycling of iron
pH homeostasis	Lungs, kidneys and brain work together in synergic manner to maintain the blood pH within normal limits to achieve acid-base homeostasis. In the blood, breathing contributes to regulation of the acid–base balance via affecting the CO_2 concentration; H+ is exchanged with sodium in the kidneys. Kidneys also adjust acid-base balance excreting or reabsorbing bicarbonate [HCO_3^-] or by decreasing hydrogen ion secretion from the tubular epithelial cells.
Glucose and protein recovery from the urine	Some of the filtrated materials such as peptides, glucose and amino acids are reabsorbed, however others are excreted to the urine

"*Temperature homeostasis*", which is also called "*thermoregulation*," refers to the mechanisms employed to maintain a constant body temperature of organisms. These mechanisms include variations in metabolic heat generation and heat exchange rates with the environment. An increase in body temperature accelerates the metabolic rate by increasing the rates of chemical reactions [28]. Sleeping is stimulated by a decrease in body

temperature, whereas an increase in body temperature initiates wakening [29]. Reasonably constant body temperatures of endothermic animals allow them to grow fast, maintain high muscular power output and have an important degree of independence from the environmental temperature [28]. Endotherms allocate a substantial fraction of the energy they harvest from the nutrients to metabolism to maintain a constant body temperature. This energy is diverted from growth, reproduction or locomotion; therefore, maintaining a constant body temperature via heat generation may be regarded as energetically wasteful. Human body temperature is a critical homeostatic parameter influencing survival, cellular function and behaviour of the central neural circuits. The optimal core temperature assures maintaining efficient enzymatic activity, but, since the energy metabolism of endotherms is higher than that of the ectotherms, the endotherms generally have faster growth rates and exert higher muscular power. The surface area/ volume ratio of an animal increases as its size diminishes; therefore, many small animals need to generate huge amounts of heat to balance the heat loss in cold environments. In cold environments, mammals may generate heat by consuming brown adipose tissue for thermogenesis [30]. Endotherms may transfer heat from their core to the environment by enlarging their veins, increasing the rate of circulation, followed by sweating and evaporation on the body surface [31]. In hot environments, birds dissipate heat from their body at a high metabolic cost by evaporative cooling via panting and gular fluttering [32]. Shivering is a mechanism for converting available muscular energy to work to prevent its conversion into heat [33].

Ectotherms do not have a homeostatic mechanism against temperature changes; therefore, they are more sensitive to environmental temperature variations than endotherms. Their body temperatures change in response to the fluctuations in the environmental temperature and ectothermy is maintained at a low energy cost [28]. At high temperatures, their enzymes configure to an active state to speed up chemical reactions leading to enhanced metabolic, locomotor, reproductive and foraging activity. However, at low temperatures, these activities slow down or stop. If food is available, ectotherms may allocate the available energy for growth or reproduction. On average, 50 % of the energy of the ectotherms is allocated to growth, while it is only 1.4 % to the endotherms [34,35]. "*Poikilothermic*" organisms, like honeybees, behave like both endothermic and ectothermic organisms under different conditions. Honeybees behave like endothermic organisms during foraging and like ectothermic organisms during resting [36].

The standard metabolic rate of animals varies with their body size, body temperature and whether an ectotherm or endotherm [28]. An increase in the level of the thyroid hormone leads to an increase in basal metabolic rate, ATP utilization and turnover, cardiac activity, thermogenesis, energy expenditure and weight loss [37]. Heat balance is achieved by an organism by balancing the amounts of heat generation and loss. Heat generation is achieved as a result of the processing of the utilization of the food in metabolism plus the forthcoming work producing sub-systems. Animals cannot convert the energy extracted from the nutrients into work with 100% efficiency. Excessive energy [heat] is rejected by the surroundings if the animals do not need to maintain their body temperature.

The difference between standard metabolic rate and maximum metabolic rate is the range of metabolic rates within which an animal functions. The maximum metabolic rate is greatly linked with the skeletal muscles. When the number of skeletal muscles is compared, the skeletal muscles of mammals, on average, are 29 % greater than those of reptiles. On the other hand, the mitochondrial membrane surface of mammals, on average, is 223% greater than those of reptiles [38].

Animals may apply strategies to reduce the energetic cost of thermoregulation, to protect themselves from the harmful effect of cold, and to survive in case of lack of food and water. These strategies are daily torpor and hibernation. Torpor is defined as a phenomenon in which many small mammals and birds [heterothermic endotherms] periodically reduce their body temperature, metabolic rate and other body functions. The heterothermic endotherms regulate their body temperature at or above a specific set point for each other by increasing their metabolic rate. The heterothermic endotherms can increase again their body temperature from low torpor body temperature by generating endogenous heat. *Hibernation* is an adaptation strategy through which some animals change their metabolism and body temperature to save energy in cold seasons. During daily inactivity or multi-day hibernation, energy expenditure is reduced [39]. As is commonly observed in birds, daily inactivity lasts for hours and is reduced by foraging and feeding. The inactivity of daytime active species occurs in the night, while that of night-active species occurs during the second half of the night and in the early morning. Ground squirrels reduce their energy expenditure by 88% throughout winter via hibernation. Throughout the hibernation period, muscular activity and activities related to digestion and excretion continue at minimal levels; fat is used as the primary energy source, urea cycle is allowed via urea recycling. In blood

and tissues, acidosis happens and metabolism is depressed. Inactivity and inadequate nutritional intake cause a decrease in the rate of protein synthesis and muscle deterioration. In energy metabolism, lipids are preferred to glucose [39]. Arousal is a phenomenon that the hibernator regains its activity and starts generating heat again. Just before the beginning of arousal, the rate of respiration and oxygen consumption increase before a measurable increase in the body temperature. The heartbeat rate also rises before the blood pressure starts to increase.

The aim of the thesis is

1. to define homeostasis in terms of thermodynamics
2. to calculate the effects of the diet-induced microbial composition of the gut on energy balance and entropy generation rate in obese and lean subjects.
3. to elucidate the lifespan entropy generation of athletes based on the dietary recommendations for four different sports and compare the results of these calculations with the statistical lifespan data.
4. to estimate the lifespan of athletes by assessing entropy generation/accumulation in human subjects when exposed to low energy availability diet and varied dietary protein intake.

This thesis involves three different research. The first part of the study is related to the effects of gut microbiota alterations depending on the diet on energy and entropy balance. Thermodynamic assessment of the lifespan of athletes doing different sports by calculating nutritional entropy creates the second part of the study. The final part of the thesis is the assessment of entropy generation/accumulation in human subjects when exposed to energy restriction, increased exercise expenditure, and varied dietary protein intake. The last part of the study was realized in Professorship for Exercise, Nutrition and Health at the Technical University of Munich thanks to TUBITAK 2214-A Fellowship Programme.

2. LITERATURE REVIEW

2.1. ENTROPY GENERATION AND ACCUMULATION IN BIOLOGICAL SYSTEMS

The term ‘entropy’ is assigned different meanings depending on the context it is used in. Thermodynamic entropy is not a measurable quantity but is calculated. In statistical mechanics, entropy is calculated in terms of the number of microscopic configurations known as microstates [40]. At the microscopic level, energy gained from low-level heat transfer induces molecular movement, friction and vibration, increases molecular kinetic energy, results in irreversibility at the macroscopic level and causes loss of potentially useful work and entropy generation. In engineering thermodynamics, entropy is regarded as the measure of the thermal energy per unit temperature that is not available for doing useful work [41]; whereas, in information technology, entropy is a measure of information [42] as frequently used in neuroscience and refers to the complexity of a system. In biothermodynamics, exergy destruction is regarded as the major cause of thermodynamic entropy generation [43]. It equals the amount of energy dissipated in the form of molecular vibrations and cannot be used to perform work [44]. In recent years, several articles have proposed the use of the entropy perspective to assess the physiological state of the human body under different physical conditions [7,43,45–47]. A fraction of the generated entropy, when accumulates in the system causes structural changes, as expressed by the ‘entropy theory of ageing [48].

Organisms are open systems operating through optimized irreversible cycles driven by entropy-generating exergy gradients. Thermal flux is driven by the temperature difference between the organism and its environment, diffusion processes driven by the concentration gradients, velocity gradients coupled with viscous stress, chemical reactions, driven by the chemical potential differences and dissipation caused by work performance via interaction with the environment are among the entropy generating living processes [49]. We may state respiration and circulation among the systems generating entropy under viscous stress and individual steps of the metabolism among the chemical potential difference-driven chemical reactions. The entropy of a system can change with respect to time either due to a net entropy transfer through the system boundaries or generation within the system boundaries as

described in Figure 2.1. In mechanical systems, entropy generation is related to their ware [50]. Similar to the machines, organisms subject to entropy generation, are becoming 'damaged' or 'worn' from use. However, they have the option of deferring or eluding this process. According to non-equilibrium thermodynamics, living beings *may offset the increasing entropic* burden of the body by exporting it to the surroundings by using energy. The organisms may maintain their function by modifying the organization of their molecules, cells and tissues and removing the waste products. The tissues may become more random and disordered during these processes, which could harm them. Referring to imaging technologies like MRI and 3D echocardiography will help quantify these alterations [51].

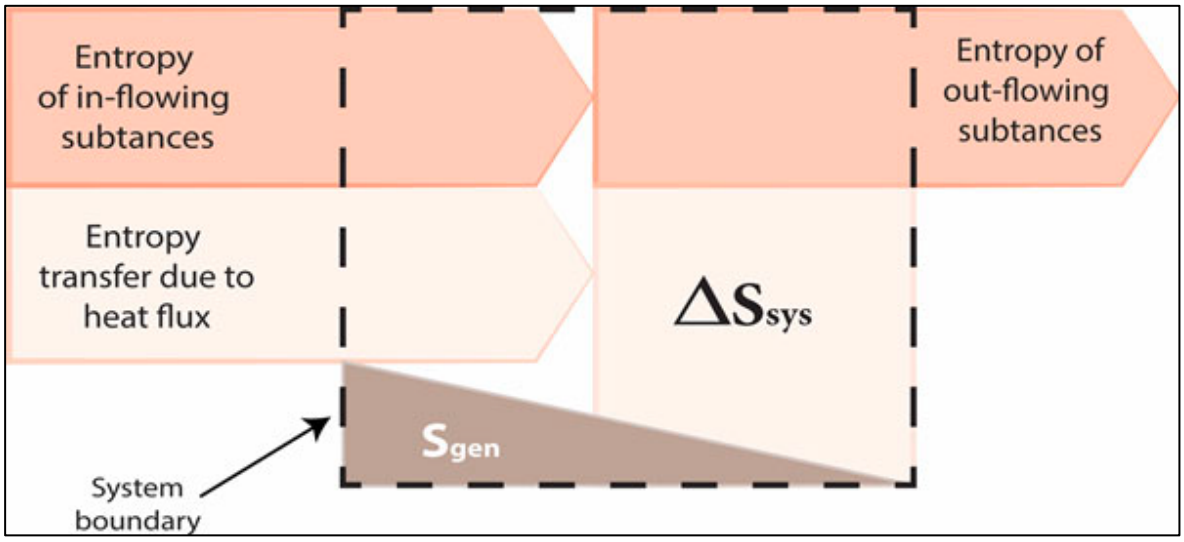

Figure 2.1. Schematic description of the entropy flow in an open system

In most energy conversion of systems, like metabolism, fraction energy is lost due to the irreversibility of systems and released to the environment as heat [52]. A chemical reaction must have a negative Gibbs free energy difference and a positive reaction entropy generation to be spontaneous [40]. Table 2.1 shows that all the glycolytic reaction stages C1–C9 has positive entropy difference, implying that they are exporting entropy. On the other hand, reactions C1 and C3 would yield negative entropy differences, and would not be spontaneous, if they are not coupled with ATP dissociation.

Table 2.1. Entropy generation in the glycolytic stages of the energy metabolism in the brain at the body temperature, i.e., 310 K (adapted from [53])

		Reactions	Entropy generation [J/mol glucose K]
Glycolysis	C1	$Glu_c+ATP_c \rightarrow G6P_c+ADP_c$	0.093
	C2	$G6P_c \rightarrow F6P_c$	0.257
	C3	$F6P_c+ATP_c \rightarrow F16BP_c+ADP_c$	0.203
	C4	$F16BP_c \rightarrow 2GAP_c$	0.040
	C5	$2GAP_c+2Pi_c+2NAD_c \rightarrow 2[13BPG]_c+2NADH_c$	2x0.118
	C6	$2[13BPG]_c+2ADP_c \rightarrow 2[3PG]_c+2ATP_c$	$2x5.48x10^{-3}$
	C7	$2[3PG]_c \rightarrow 2[2PG]_c$	2x0.01
	C8	$2[2PG]_c \rightarrow 2[PEP]_c+2[H2O]_c$	2x0.087
	C9	$2PEP_c+2ADP_c \rightarrow 2PYR_c+2ATP_c$	2x0.032
Overall glycolysis		Glu_c+2Pi_c $2ADP_c+2NAD_c \rightarrow 2PYR_c+2ATP_c+2NADH_c+2H_2O$	0.253+0.846= 1.099

The term "internal work" refers to all types of work carried out within a living body, such as the electrical work carried out by the nervous system and synthesis of the entire mass of muscles and bones, as well as work carried out by the heart for blood pumping, the lungs for respiration, the liver for chemical activities, the kidneys for re-absorption and secretion processes, etc. [43]. External work is described as the other work that can be observed with the naked eye from the outside of the system boundaries (e.g., such as treadmill activity, running, etc.). There is common knowledge that work output proportionally relates to heat dissipation in an irreversible process. One of the causes of entropy production inside the confines of a living system is the inefficiency or irreversibility of the internal task performance. Some of the most prominent instances of irreversibility in biochemical processes are heartbeat, food catabolism, the activity of the Na+/K+ pump, gene network, etc. [54]. In a thermodynamically irreversible process, obtainable work is always lower than that of a theoretically reversible process. The difference is dissipated as heat and converted into entropy. As a non-equilibrium thermodynamic framework, the existence of vitality throughout the boundary of a living framework is essential to digestion.

Entropy generation during external work performance may vary with mass input and output throughout the system. It may also vary with entropy accumulation in the system and the system boundary temperature. Muscle work performance is determined by physiological conditions and by the efficiency of ATP (or substrate) utilization in the ion pumping process, which is internal work [55]. *Two major paths are followed by research on ageing: one focuses on the biological nature of ageing and employs highly advanced experimental observation techniques to determine how and why cells age.* By employing advanced mathematical analysis, another major path exploits the fundamental principles of thermodynamics to investigate the nature of the same phenomena. The development of experimental techniques made it possible to trace the consequences of ageing-related changes in the morphology of cells [56,57]. The process of gene-level ageing occurs in the body as a result of DNA strand distortion [58]. Cells attempt to counter this process by destroying the mutated strands [59], preventing them from spreading. Telomere-induced cellular ageing theory suggests that there is a gene-level built-in program that triggers cell death to prevent mutations from spreading. Telomere-induced cellular ageing theory suggests that there is a gene-level built-in program that triggers cell death to prevent mutations from spreading [60]. It is believed that this program is responsible for the natural ageing process we all experience through.

A fraction of the entropy, which is generated via metabolic heat generation, accumulates in the body and reveals itself as ageing [61]. The 'entropic ageing' hypothesis postulates that age-related alterations overwhelm the body's repair mechanisms and result in the loss of molecular functioning [62–65]. Silva and Annamalai [48] and Annamalai and Silva [66] quantified the stress-related impacts of entropy formation on certain organs. DNA damage is the most important impediment in the ageing process [67–69]. All living beings die after generating a precise amount of “lifespan entropy” considering their bodies cannot tolerate accumulating extra harm after exceeding the lifespan entropy era restriction.

Living organisms maintain a state of high organization [2], and entropy accumulation implies increasing disorder or structural impairment [70]. The balance between these activities can be maintained in favour of the working molecules by genetically triggered repair and replacement processes [59,64], but as people age, this balance shifts in favour of inactivation and malfunctioning [65]. Both theories and data support [71] the notion that certain processes during ageing increase cellular entropy [72,73]. Energy is required to avoid

entropy formation and repair the accumulated damage in dissipative systems, which behave in the same way [1]. As explained by Yalçınkaya *et al.* [74] with the decline of mitochondrial energy generation, organisms start experiencing structural impairment. Living organisms are far from equilibrium structures, and they have a great tendency for approaching equilibrium, which implies ageing and increased entropy. To survive far from equilibrium, a living being should develop an entropy gradient with their surroundings. Such gradients are maintained only by utilizing energy imported from outside, so an open system may move away from near towards far from equilibrium.

The lifespan entropy generation was related to the heat loss from the body, the level of physical activity and the composition of the diet [48,75]. Çatak *et al.* [76] suggested referring to the lifespan entropy generation by the masseter muscle during chewing as an indicator of life expectancy. Their criterion showed that the life expectancy of an obese person was much shorter than those of non-obese individuals. Kuddusi [77] computed the lifetime entropy generation per unit mass of a person and discovered a significant variance in their life expectancy after noting that people in different parts of Turkey have varied eating habits.

2.2. EFFECTS OF GUT MICROBIOTA ON ENERGY HOMEOSTASIS

Millions of microorganisms live on and in the human body. These microorganisms and combined microbial genomes interact with the human host. Therefore, scientists of the 21st century put forward "the ideas of human superorganism" against to "human pure organism idea" [78–81]. Dietert [81] said, "Human being is a superorganism" and resembled the human microbiome to rain forest in his book 'The Human Superorganism: How the Microbiome Is Revolutionizing the Pursuit of a Healthy Life'. The human superorganism [70 kg] includes approximately 10 times more cells of microorganisms (3.8×10^{13}) in comparison to nucleated human cells (3.0×10^{12}) [82]. Figure 2.2. represents human superorganisms.

Lederberg and McCray [83] defined the term 'microbiome' as "the ecological community of commensal, symbiotic, and pathogenic microorganisms that share our body space and have been all but ignored as determinants of health and disease" but this definition means the term of 'microbiota' not microbiome [84,85]. The microbiome was defined as the collective genome of microorganisms within the body [86]. According to a metagenomic

study by Quin *et al.* [87], the human gut microbiome includes 3.3 million microbial genes; this number is 150 times higher than the human's own genome. Gut microbiota refers to the microorganisms living in the gastrointestinal tract such as bacteria, viruses, fungi, and archaea, which have co-evolved with the host and are in a mutualistic relationship with the organism [88]. Firmicutes and Bacteroides are the most known bacterial phyla among the gut microbiota species. Bacteroides constitute approximately 20-25% of the gut microbiota and are composed of three large classes of Gram-negative, non-spore-forming, anaerobic or aerobic and rod-shaped bacteria. Firmicutes constitute approximately 60-65% of the gut microbiota; they comprise over 250 genera, including Lactobacillus, Streptococcus, Mycoplasma, and Clostridium, which can produce several short-chain fatty acids like butyrate. Proteobacteria constitute approximately 5-10% of the gut microbiota. They include a wide variety of pathogens, such as Escherichia, Salmonella, Vibrio, Helicobacter, Yersinia, Legionellae and many other notable genera. Actinobacteria constitute approximately 3% of the microbial population in the gut [89,90]. Actinobacteria that are gram-positive consist of six classes; Actinobacteria, Acidimicrobiia, Coriobacteriia, Nitriliruptoria, Rubrobacteria, and Thermoleophilia [91].

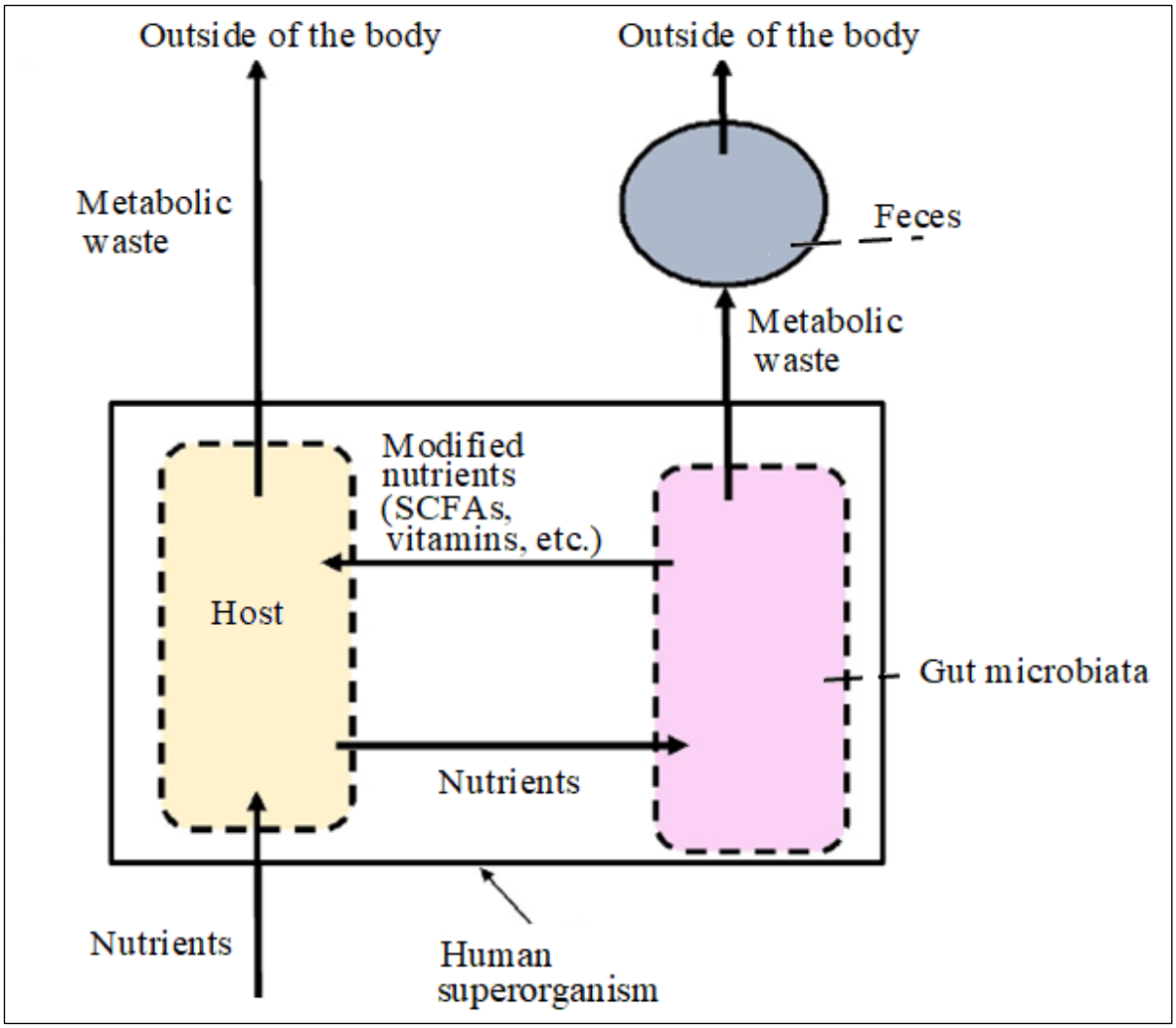

Figure 2.2. Schematic description of interacting subsystems of human superorganism

Eli Metchnikoff put forward that "The dependence of the intestinal microbes on the food makes it possible to adopt measures to modify the flora in our bodies and to replace the harmful microbes with useful microbes" [92]. For example, the Bacteroides enterotype grows up with animal protein and the Prevotella enterotype increases when the diet contains more carbohydrates and monosaccharides [93]. Low-fibre and high-animal protein, saturated fat, and carbohydrates diet cause an increase in proportions of Firmicutes and Proteobacteria. However, a higher-fibre and plant polysaccharides diet enables an increase in diversity and proportion of Bacteroides and Actinobacteria [94].

Recent studies have suggested that the microbial composition of the gastrointestinal tract alters as related to dietary habits and nutrients. The ratio of microbial species changes due to dietary composition and time of diet application time [95–97]. The Mediterranean diet

contains a large portion of fresh fruits and vegetables, olives, legumes, seeds, and tree nuts. Olive oil is the main source of additional fat and the intake of seafood, fish and eggs is reduced and the intake of milk and milk products is limited to a few times per week. However, alcohol, red meat and its products are low limits in this diet [98]. Haro *et al*. [99] designed a study to observe alterations in the gut microbiota of an obese population that consumed a Mediterranean diet or a low-fat, high-complex carbohydrate diet for one year. As the result of this study, a decrease in the Prevotella genera and an increase in the Roseburia and Oscillospira genera which are butyrate producers in the Firmicutes phylum and play a role in the development of the immune system [100] after the consumption of the Mediterranean diet were observed. The Western diet consists of dominantly refined cereals, sugars, corn, and potatoes as carbohydrate sources and refined vegetable oil, fatty domestic meats, and high amount of salt [101]. Agus *et al.* [102] found that a Western-type diet causes a high increase in pro-inflammatory Escherichia coli bacteria in the gut microbiota of mice. Vegetarian diets do not include any kind of meat or meat products. The vegan diet is a subclass of a vegetarian diet that does not contain any products based on animals such as eggs, milk and milk product except meat and meat products [103]. Vegetarian diets consist of a high amount of carbohydrates, dietary fibre, n-6 fatty acids, carotenoids, and low amounts of protein, long-chain n-3 fatty acids and saturated fat [104]. Zimmer *et al*. [105] observed that Bacteroides spp. and Bifidobacterium spp. were lower in vegetarian subjects comparison with control groups whereas Bacteroides spp., Bifidobacterium spp., *Escherichia coli*, and bacteria belonging to Enterobacteriaceae family were lower in vegans when compared with controls. The ketogenic diet is defined as a diet containing low carbohydrates, high fat and sufficient protein [106]. Olson *et al.* [107] found that in mice gut, the ketogenic diet increased the relative abundance of *Akkermansia muciniphila* classified as the only gram-negative symbolic Verrucomicrobia and can produce mucin-degrading enzymes [108]. It was specified that the ketogenic diet also caused an increase in Parabacteroides, Sutterella, and Erysipelotrichaceae in mice gut. Another diet type is the gluten-free diet which has been mostly applied. The gluten-free diet involves foods that do not contain gluten such as legumes, corn, rice, meat and meat products, and fresh fruits and vegetables, unlike foods including gluten such as wheat, barley, and rye [109]. De Palma *et al*. [110] investigated the impact of the gluten-free diet on the gut microbiota in ten healthy subjects whose ages are average of 30.3 years. In his part of the study, the subjects consume a gluten-free diet and then their faecal samples were analysed. It was found that a gluten-

free diet decreased the Lactobacillus, Bifidobacterium, Bifidobacterium longum, *Feacelibacterium prausnitzii,* and *Clostridium lituseburense* proportions and increased *Escherichia coli* and Enterobacteriaceae counts.

Macronutrients consist of carbohydrates, fats, and proteins. Macronutrients that enable energy to the body are key components of diets [111]. Fats supply 80% of the energy while carbohydrates and protein provide 5-18% and 2-5% of the energy, respectively [112]. Daily carbohydrate intake should be 130 g/d for adults and children. Fat should be taken daily at 0.80 g/kg for adults. Protein consumption should be 0.8 g/kg /d for adults [113]. The composition and amount of macronutrients affect gut microbiota composition [114].

Gut microbiota composition changes with the amount and type of protein in the diet. It was found that a high-beef diet increased Bacteroides spp. and Clostridia spp. whereas a meatless diet decreased *B. adolescentis*. Fats consist of two types of fatty acids: saturated and unsaturated fatty acids. The composition of dietary fat influences the gut microbiota [115]. It was shown that the high-fat diet including the lard diet reduced *Akkermansia muciniphila*, Lactobacillus, and Bifidobacterium portions in mice in comparison with the isocaloric high-fat diet including fish oil [116]. The type and amount of carbohydrates in the diets affect gut microbiota composition. Villasante *et al.* [117] found that counts of Planctomycetes, Planctomycetia, Planctomycetales and Lactococcus were higher in *Salmo salar* fed the high carbohydrate [containing 30% wheat starch]/low protein diet in comparison with *Salmo salar* fed the medium carbohydrate [containing 15% wheat starch]/medium protein diet. Diets rich in protein and animal fat lead to an increase in Bacteroides spp. whereas high consumption of carbohydrates causes an increase in Prevotella spp. in gut microbiota composition [96].

Physical exercise also affects gut function and the gut microbiome. Anti-inflammatory, anti-apoptotic, and antioxidant systems are mostly related to the sustainability of redox balance, the energetic buffer, and mitochondrial biogenesis stimulated by aerobic exercise supporting the regulator of several metabolic diseases [118]. Barton *et al.* [119]] found that the genus *Erysipelotrichoceae incertae sedis* existed in relatively higher proportions in the athlete's group when compared with sedentary low-BMI and high-BMI groups. It is suggested that athlete microbiome improved the capability of harness energy and tissue repair from the diet by increasing the ability of carbohydrate metabolization, cell structure and nucleotide biosynthesis as a reflection of high energy demands and cell turnover in elite sport. Petersen

et al. [120] suggested that the abundance of *Methanobrevibacter smithii* was higher in professional cyclists in comparison with amateur cyclists. *M. smithii* increases energy efficiency in the host by regulating carbohydrate and energy pathways. Petersen *et al.* [120] also claimed that exercise intensity, duration of exercise, type of exercise, diet, and host metabolism influence athlete microbiomes. Irregular, long-lasting, and exhausting physical exercise may cause dysbiosis in gut microbiota and thus impaired immune response leading to health problems for athletes [121].

Gut microbiota has main functions involving metabolic actions that are related to energy harvest and nutrient absorption, crucial trophic influences, and the protection of the colonized host from attacks of pathogen microorganisms [122]. Gut microbiota and human diseases affect each other reciprocally. It means that the composition and activities of gut microbiota may cause disorders of any organs, tissues, and cells and some diseases may lead to alterations in gut microbiota composition and activities [123]. The gut microbiome is associated with the maintenance of homeostasis and the evolution of human diseases such as cancer, obesity, neurological disorders, and inflammatory bowel diseases [124].

A large number of metabolites are produced by gut microorganisms that interconnect with cells of the enteric nervous system, mucosal immune system, and endocrine system and circulate and reach various metabolic organs such as the liver, brain, pancreas, skeletal muscles, and brain and affects metabolic functions [125]. Gut microbes have enzymes to digest microbiota-accessible carbohydrates such as cellulose and resistant starch, which cannot be digested by humans [126,127]. SCFAs such as acetate, propionate, and butyrate are produced by bacteria as a result of the fermentation of microbiota-accessible carbohydrates. SCFAs both enable energy production, gluconeogenesis, and lipogenesis and can regulate the physiological process by supplying signalling molecules [128]. SCFAs are used via the gastrointestinal membrane and released to different tissues. SCFAs can participate in the tricarboxylic acid cycle to produce ATP. SCFAs play a role as signalling molecules, which can control host metabolic pathways to sustain a healthy state in the gastrointestinal tract [129]. SCFAs have anti-inflammatory effects. They increase the regulatory T lymphocytes, decreases the production of the pro-inflammatory cytokine, and stimulate the secretion of some hormones such as oxytocin, serotonin, testosterone, and T4 hormone [130]. Butyrate enables the regeneration of intestinal cells to the reparation of the intestinal mucosa and triggers the secretion of intestinal mucin glycoprotein [131]. Butyrate

increases insulin sensitivity, decreases adipose tissue inflammation, and stimulates thermogenesis and energy expenditure apart from glucose tolerance [132]. Acetoacetate produced as a result of the metabolization of butyrate in the liver is the main fuel resource of intestinal cells. More than 70% of oxygen consumption occurs in isolated colonocytes because of butyrate oxidation. Propionate and acetate are two essential SCFAs for gluconeogenesis and lipogenesis, respectively. Propionate contributes to the improvement of insulin sensitivity and prevents hepatic glycogenesis from lactate [89]. Acetate may contribute to the control of central appetite control. It is necessary for the growth of some bacteria and it plays a role in lipogenesis and cholesterol metabolism [133].

Trimethylamine is one of the specific products produced by the gut microbiota. Trimethylamine is produced as a result of dietary quaternary amines [especially choline and L-carnitine] metabolism of gut microbiota and it is converted into trimethylamine N-oxide by flavin monooxygenase 3 in the liver. Trimethylamine N-oxide level in the plasma depends on the genetic variation of gut microbiota and the composition of the consumed diet. It is associated with atherosclerosis and atherothrombotic cardiovascular disease. Trimethylamine N-oxide may provide the formation of a foam cell by regulating the macrophage scavenger receptors into up, inducing deregulation of metabolism of enterohepatic cholesterol and bile acid and damaging transport of macrophage reverse cholesterol [134,135].

The other gut microbial metabolite indolpropionic acid is the product of tryptophan metabolism. Indolpropionic acid shows a strong anti-non-alcoholic steatohepatitis effect. Indolpropionic acid modulates the microbial composition in the gut and inhibits gut microbial dysbiosis. Indolpropionic acid induces the expression of ZO-1 and Okcludin proteins and continues the gut epithelium homeostasis by enabling a decrease in the plasma endotoxin levels. Indolpropionic acid prevents the signalization of NF-κB and suppresses liver inflammation and damage by reducing levels of TNFa, IL-1β, and IL-6 pro-inflammatory cytokines. Indolpropionic acid relieves non-alcoholic steatohepatitis phenotypes induced with the diet and plays a role in the inhibition of expressions of the collagen and fibrogenic genes [136]. Besides, indolpropionic acid is related to type-2 diabetes. It was found that there was a negative correlation between the indolpropionic acid level and type-2 diabetes incidence and inflammation grade. The consumption of dietary

fibre is correlated with indolpropionic acid [137]. Indolpropionic acid also has anti-tuberculosis effects [138].

Lipopolysaccharides are produced by gram-negative bacteria and their transport of them occurs via chylomicrons. Lipopolysaccharides level is negatively correlated with the survival rate in peritoneal dialysis patients. Levels of lipopolysaccharides may indicate inflammation and it may be beneficial for prognosis [123].

Gut microbiota affects the regulation of the energy balance of the host [139,140]. The gut microbiome increases energy production and causes maximize the energetic value of food. Besides, it enables to provide biosynthetic pathways and supports the homeostasis of the host [141]. Gut microbiota simplifies deposition and storage of fat in adipocytes by suppressing intestinal extraction of an inhibitor of lipoprotein lipase referring to a fasting-induced adipose factor called Angiopoietin-like 4 (ANGPLT4). Lipoprotein lipase acts a role in converting triglycerides into fatty acids via the hydrolysis process, the fatty acids are conveyed into adipocytes, then re-esterified into triglycerides and stored as fat in the adipose tissue. ANGPLT4 achieves its antiobesogenic function by provoking lipoprotein lipase activity, hence its activity increases by suppression of ANGPTL4 by the microbiota, and this causes an increase in cellular intake of fatty acids and accumulation of triglycerides in adipocytes [142]. The SCFAs signal through the central nervous system and some G protein-coupled receptors (GPCRs) in order to regulate the physiological process, particularly energy homeostasis, lipid and carbohydrate absorption, and suppression of inflammatory signals. The GPCRs are also called free fatty acid receptors (FFAR2 or GPR43 and FFAR3 or GPR41). Acetate stimulates FFAR2, propionate stimulates FFAR2 and FFAR3 and butyrate stimulates FFRA3 [143]. The FFAR2 is secreted primarily from the immune cells and adipocytes and has a significant role in energy homeostasis. The SCFAs are related to the activation of FFAR2 in the adipose tissue and cause suppression of insulin signalling and reduction of lipid storage in the adipocytes apart from an increase in lipid oxidation in the other tissues, thus resulting in rising energy expenditure [144]. Propionate stimulates leptin production through FFAR2 stimulation in white adipose tissue and human omental and abdominal tissues. Omentum is the large membrane in the abdominal cavity that connects and supports the internal organs. Within the intestines, the SCFA-mediated FFAR3 triggers the release of the PYY. The FFAR2 is activated by propionate and increases the heart rate, energy metabolism and secretion of norepinephrine [126]. The SCFAs enable the triggering

of the gut peptides, such as GLP-1 and PYY by interacting with the brain, thus contributing to the regulation of appetite [88,145,146].

In general, a system is pushed out of equilibrium and the irreversible mechanisms that produce entropy start to work when it starts exchanging entropy with its surroundings. Entropy is exchanged by gut bacteria with faeces together with heat and matter (Figure 2.2). In an adiabatic system, entropy flowing out is always greater than entropy flowing in. The discrepancy is the result of the system's irreversible processes producing entropy. Entropy is produced with metabolism in the current investigation in both the host and the gut microbiota sub-systems [147]. Human gastrointestinal microbiota, which is also known as gut microbiota, live in the digestive tracts of humans. The gut microbiota is established in about one to two years after birth, by which time the intestinal epithelium and the intestinal mucosa barrier are co-developed in a supportive way of the gut flora and that also provides a barrier to pathogenic organisms [148,149]. The inner and outer mucus layers of the digestive tract are dynamic compartments. The outer layer is degraded by the microbiota and transported with the intestinal content while being constantly replenished from the inner layer [149].

2.3. THE EFFECT OF ENERGY INTAKE AND DIET COMPOSITION ON ATHLETES' HEALTH

The longevity of an athlete is determined by the diet he/she is consuming, and the intensity of the dynamic or static exercise he or she is performing [150–155]. In dynamic exercise, moderate muscle length changes and moderate joint movement through rhythmic contractions cause moderately small intramuscular force changes. Static exercise does not involve muscle length alterations or joint movements, it is based on the expansion of a moderately small intramuscular force with little change in muscle length. Classification of sports based on the fraction of their static and dynamic components is shown in Table 2.2. The increase in the dynamic component is defined in terms of the estimated percentage of peak oxygen uptake achieved that results in increased cardiac output. An increase in the static component is associated with an estimated percentage of maximally achieved voluntary contraction of the muscle, resulting in an increase in blood pressure [156,157].

Dynamic exercise causes an increase in oxygen demand, arterial pressure and cardiac output due to high metabolic demand in the contracting muscle. Likewise, blood pressure and

oxygen uptake increase with static exercise [158]. The high jumpers and marathon runners usually have low body weights and tend to live longer than the general population, on the other hand, 100 m sprinters are believed to live less than the general population. Within this context, powerlifters are seen to have the shortest life expectancy mainly because of their high body weight [159]

Table 2.2. Classification of sports based on their static and dynamic components. Summarized by Mitchell and Wildenthal [158].

	LOW DYNAMIC COMPONENT (<40% Max O_2)	MODERATE DYNAMIC COMPONENT (40-70% Max O_2)	HIGH DYNAMIC COMPONENT (> 70% Max O_2)
HIGH STATIC COMPONENT (>50% MVC, maximal voluntary contraction)	Gymnastics, Sailing Windsurfing, Weight lifting	Skateboarding, Wrestling, Snowboarding, Bodybuilding	Boxing, Canoeing/Kayaking, Cycling, Rowing
MODERATE STATIC COMPONENT (20-50% MVC)	Archery, Auto racing, Diving, Motorcycling	Rugby, Figure skating, Surfing, Running (sprint)	Basketball, Swimming, Running (middle distance), Handball
LOW STATIC COMPONENT (<20% MVC)	Billiards, Bowling, Golfing, Curling	Baseball/Softball, Table tennis, Volleyball, Fencing	Badminton, Race walking, Soccer, Tennis

Endurance athletes such as runners, cross-country skiers, swimmers, and cyclists must come over extreme physiological conditions that lead to an imbalance in the inner body's homeostasis, overwhelming organs and abnormal functions in the system. The long-term, physical effort at too high levels results in a defence response of the whole body by hormone secretion, acute phase-protein synthesis, and shifts in liquid and metabolic balance. The fundamental adaptations to endurance exercises are the amelioration of mechanical, metabolic, neuromuscular, and contractile occasions, a re-balance of electrolytes, a reduction in glycogen storage, and an increment in mitochondrial biogenesis in muscle tissue. Moreover, endurance exercises impact significantly intestinal permeability, oxidative stress, muscle damage, immune responses, and systemic inflammation. To re-regulate homeostatic balance as a response to an increase in body temperature changing blood flowing and

increasing dehydration, the body releases adrenaline and glucocorticosteroids (review from [160]).

A cornerstone of sports nutrition is meeting energy needs, preventing disease and bodily injuries, and improving performance. A balanced energy intake relative to the expenditure of training and competition protects the body from energy deficiency and accumulation of excessive body fat stores [161]. Athletes should consume adequate amounts of carbohydrates, lipids, and proteins in addition to fluid, vitamins, and minerals in order to fuel their training as well as their basic energy requirements [162]. The energy demand of athletes is affected by the training period, competition cycle, and exercise intensity. Exposure to heat or cold, stress, and some physical injuries also change energy requirements. Based on metabolic rate requirements, energy demands decrease with age [163].

Energy availability (EA) is critical to sustaining the body's physiological functions, especially for athletes. It can be determined by subtracting exercise energy expenditure (EEE) from dietary energy intake (EI) as a function of lean body mass (LBM)[164]. In terms of bioenergetics, the EA concept posits that after the energy demands of exercise have been met, the remaining dietary energy intake is available for other physiological functions such as thermoregulation, growth, cell maintenance, reproduction, and immunity [165]. As a consequence, a state of low energy availability (LEA) can be the result of suboptimal dietary EI such as in the state of caloric restriction (CR), high levels of exercise energy expenditure, or a combination of both in athletes. In the state of LEA, sufficient energy is not available for the maintenance of physiological functions in the body and optimal health of the body [166]. For an athlete, LEA can lead to impairment in the energy homeostasis mechanism by triggering metabolic and hormonal responses. LEA may affect leptin secretion, suppress hypothalamic-pituitary-thyroid and hypothalamic-pituitary-gonadal axes, reduce bone formation and increases bone reabsorption, and decrease skeletal muscle protein synthesis [164]. Athletes need a certain amount of calories and nutrients to have a determined amount of muscle percentage. On the other hand, the muscle structure can be impaired and the body can try to repair muscle structure by obtaining necessary vitamins and minerals from bones

LEA can be defined as energy availability under 30 kcal /kg FFM (fat-free mass)/ day [167]. In exercising men, 15 kcal/kg. FFM/day can cause a reduction in insulin, leptin, and fasting glucose while leading to an increase in glycerol and fatty free acid (FFA) concentrations [168]. Moreover, LEA in nulliparous female athletes can result in urinary incontinence apart

from other health problems related to bone health, immune function, metabolism, cardiovascular problems, etc. [169]. For young adult women, the optimal EA is 45 kcal/kg FFM to maintain their physiological functions such as metabolism, and reproduction. EA under this value can be considered an undernutrition state that is the circumstance of a lack of macronutrients, vitamins, and minerals [170].

Energy balance is defined as the difference between energy intake and total energy expenditure (TEE) consisting of resting metabolic rate (RMR), non-exercise activity (NEAT), diet-induced thermogenesis (DIT), and exercise [165]. The energy balance is related to energy expenditures that lead to the change in body weight and/or body composition. On the other hand, EA is associated with exercise energy expenditure and is necessary for sustaining physiological functions [164]. Energy balance is also vital for elite athletes to enable a healthy body weight and fat level, growth, and prevent any injury risk [171].

The amount and type of diet and exercise type and intensity affect athletes' longevity by depending on their metabolism. The effects of LEA on the body are well-known, while it is unknown how LEA affects lifespan. A caloric restriction (CR) diet is one of the reasons for LEA [166] several studies claimed that a CR increases lifespan [75,172–175] but a CR diet should not be higher than % 20 CR than a weight-maintaining diet [176]. CR diet resulting in LEA may cause alterations in metabolic response in the human body and thus affects the athlete's longevity. The intensity of exercise is another reason LEA influences, an athlete's longevity by impacting energy demand and metabolic activity [177]. The effects of LEA due to CR diet and high exercise intensity on the body are well-known, while it is unknown how LEA affects lifespan [75,172–175]. However, there is no study in the literature that shows the impact of long-term CR on the human lifespan. The diet, exercise, metabolism, and ageing relationship may be explained by biothermodynamics Athletes obtain energy from food by metabolization of macronutrients to meet the energy requirements for doing sports. Energy conversion in living bodies is induced by the metabolic process at the cellular level, through biochemical reactions and, along with other vital functions, providing the necessary heat to keep core body temperature, as well as providing the energy necessary for muscle effort and movement [178]. These chemical reactions take place via two main metabolic pathways. These ways; catabolic pathways (catabolism) in which large-molecule substances turn into smaller-molecule ones, and anabolic or biosynthetic pathways in which small

molecules are called anabolism, which is necessary for the formation of cellular material, turn into large-molecule substances. All catabolic pathways are oxidative and therefore they lead to produce energy, while biosynthetic pathways are reductive and consume energy. Metabolism, thus, involves whole energy conversion and transfer mechanisms based on thermodynamics [179].

In the case of energy deficiency in the system, which will occur as a result of energy restriction and increased energy expenditure, changes occur in the body's anabolic metabolism [180]. Changing energy inputs and outputs in the system will affect catabolic and anabolic metabolism. Alterations in the metabolic response may cause an increase in the entropy generation rate by triggering more heat dissipation. Therefore, athletes' longevity may be impacted. In this study, we aimed to examine the relationship between energy balance, exercise, and nutritional composition of the diet in terms of thermodynamics and their effects on the average lifespan of athletes that consume three different diets control diet (CON), calorie restriction-low protein diet (LEA-LP), calorie restriction-high protein diet (LEA-HP). Thus, we tried to assess whether LEA and a high-protein diet affect an athlete's lifespan in terms of thermodynamics.

3. MATERIALS AND METHODS

3.1. THERMODYNAMIC BALANCE EQUATIONS

For thermodynamic analysis, first of all, the material inputs and outputs within the system boundaries should be determined. As shown in Figure 3.1, the amount of food and water consumed and the amount of oxygen inhaled represent the mass of matter entering the system, while the amount of urea and faeces removed from the system with carbon dioxide and water resulting from catabolic metabolism represent the amount of mass leaving the system. Using the mass balance Equation (3.1), the number of faeces and urea leaving the system can be estimated and compared with the real test data.

$$\sum_{in} \dot{m}_{in} - \sum_{out} \dot{m}_{out} = \frac{dm_{system}}{dt} \tag{3.1}$$

where $\sum_{in} \dot{m}_{in}$ and $\sum_{out} \dot{m}_{out}$ imply the total mass entering into the body and leaving from the body. $\frac{dm_{system}}{dt}$ defines the mass change in the body with the time.

Calculations were performed based on the metabolism of glucose, palmitic acid and average amino acids representing carbohydrates, lipids and proteins. It would be extremely difficult to use every carbohydrate, lipid and protein of nutrients for this purpose. Therefore, applying the 80%-20% rule as described by Özilgen [19], it is aimed to obtain 80% of the modelling benefits within 20% of the difficulty level. Accordingly, the energy balance Equation (3.2) will be used specifically for the metabolism reactions of glucose, palmitic acid and average amino acids (see Equation (3.4)-(3.6)).

$$\sum_{in} [\dot{m}\,[h + e_p + e_k]]_{in} - \sum_{out} [\dot{m}\,[h + e_p + e_k]]_{out} + \sum_{i} \dot{Q}_i - \dot{W} = \frac{d\left[m\left(u + e_p + e_k\right)\right]_{system}}{dt} \tag{3.2}$$

$\dot{m}$, h, e_p, e_k , $\dot{Q}_i, \dot{W}$ and u in the equation represent the mass, specific enthalpy, potential energy, kinetic energy, heat, work, and internal energy of matter entering or leaving the system in unit time, respectively. $\frac{d\,[\,m(\,u+\,e_p+e_k)]_{system}}{dt}$ implies energy accumulation in the

body with the time and there is no energy accumulation for healthy organisms. The human body is considered a steady-state system. Therefore, we neglect kinetic and potential energy in the calculations.

The mathematical formulation of the entropy balance as described by the second law is:

$$\sum_{in}[\dot{m}\ s]_{in} - \sum_{out}[\dot{m}\ s\ ]_{out} + \sum_{i}\frac{\delta\dot{Q}_i}{T_{b,i}} + \dot{S}_{gen} = \frac{d[\ m\ s]_{system}}{dt} \qquad (3.3)$$

where, $\frac{d[\ m\ s]_{system}}{dt}$ is entropy accumulation, i.e., structural impairment, within the system, $\sum_{in}[\dot{m}\ s]_{in}$ and $\sum_{out}[\dot{m}\ s\ ]_{out}$ are the entropy inflow and outflow masses entropy through the system boundaries; $\sum_i \frac{\delta\dot{Q}_i}{T_{b,i}}$ is the rate of the entropy transfer with the heat released from the system, where $\delta\dot{Q}_i$ is the differential amount of the heat transfer rate, which is not available for doing work; $\dot{S}_{gen}$ is the entropy generated within the system, and T_b is the temperature of the system at the boundary.

$$C_6H_{12}O_6 + 6O_2 \longrightarrow 6H_2O + 6CO_2 \qquad (3.4)$$

$$C16H_{32}O_2 + 23O_2 \longrightarrow 16CO_2 + 16H_2O \qquad (3.5)$$

$$C_{4.57}H_{9.03}N_{1.27}O_{2.25}S_{0.046} + 4.75O_2 \longrightarrow 3.245H_2O + 3.935CO_2 + 0.635CH_4N_2O \qquad (3.6)$$

Living systems [especially triacylglycerol stores in adipocytes] maintain a non-equilibrium state, and the kinetics of enzymes that catalyze hydrolysis and resynthesis reactions regulate the degradation rates of high-energy compounds. In systems that do not reach equilibrium, the application of the laws of thermodynamics is restricted [181]. Equations (3.1)-(3.3), whose equations are given above and used for thermodynamic calculations in living systems, are considered and evaluated in relation to the chemical reactions whose Equations (3.4)-(3.6) are given above.

Describing the metabolism with Equations (3.4)-(3.6) is an oversimplification, during exercise lactic acid accumulates in the muscles of the athletes, and then it is reused. Energy, e.g., enthalpy, extracted from carbohydrates will not be affected by lactic acid accumulation and its reuse in the muscles, since enthalpy is a state function and its value depends on the initial, carbohydrates and the oxygen, and the final chemical species, e.g., carbon dioxide and water [40]. Ulu *et al*. [176] while discussing energy storage and reuse in biological

systems reported that entropy generation associated with this phenomenon is extremely small and does not contribute to the lifespan entropy accumulation; therefore, entropy generation during lactic acid utilization and reuse in the muscles are neglected.

In the present study, calorie uptake with each food is calculated in terms of their enthalpies exactly the same way as Öngel *et al.* [182]. The molecular structures in biological systems are often so complex that it is typically necessary to determine their thermodynamic characteristics using the group contribution approach as they are not easily accessible in tables [183]. Joback and Reid [184] recommendations for group contribution approaches are the most well-known. Using this approach, a complex biological structure is broken down into the chemical subgroups that contribute to it, and the thermodynamic characteristics of each subgroup are then assessed independently. Calculating a complicated chemical structure's thermodynamic characteristics requires adding the thermodynamic characteristics of each of its subgroups. For instance, sucrose, a disaccharide made up of the monosaccharides fructose and glucose, is an example. The group contribution technique calculates the conventional enthalpies of formation for glucose and fructose to be -1.271 kJ/mol and -1.265 kJ/mol, respectively. By combining these values, the enthalpy of formation for sucrose is calculated to be -2.536 kJ/mol. The enthalpy of sucrose production is listed in thermodynamic tables as -2.226 kJ/mol. The estimated and empirically discovered values varied by around 12%. When performing such calculations, only metabolizable chemicals are used. The estimate excludes substances in food that can be consumed. The thermodynamic parameters of fructose, glucose, and sucrose are listed in the table. All three sugars have very straightforward structures. However, extremely complex structures can only be used in conjunction with the group contribution method [184].

By assuming that the nutrient intake into the body is at 25°C, and H_2O and CO_2 exit at 37 °C, the enthalpy of the system was calculated via Equation (3.7). Enthalpy of the system around a human body is**:**

$$\Delta\dot{H} = \sum n_p\left(h_f^{-^\circ} + h^- - h^{-^\circ}\right)_p - \sum n_r\left(h_f^{-^\circ} + h^- - h^{-^\circ}\right)_r \qquad (3.7)$$

where $\Delta\dot{H}$ is the enthalpy release via Equation (3.7), n_p and n_r represent the mole number rates of the products output from and the reactants input to the system, respectively; parameters $h_f^{-^o}$, h^- and h^{-^o} are the formation enthalpies at the standard conditions. The

thermodynamic properties of the compounds are shown in Table 3.1. It was assumed that 32, 106 and 8 moles of ATP were created by the metabolism of one mole of each of glucose; palmitic acid, and the average 20 amino acids, respectively. Total work achieved by the formation of the ATP molecules was found with Equation (3.8); 34.6%, 32.2% and 10.4% represent the metabolic efficiency (η) of glucose, palmitic acid, and the average of 20 amino acids, respectively [48,66].

$$\dot{W}_{ATP} = \eta \Delta \dot{H} \tag{3.8}$$

where, $\dot{W}_{ATP}$ represents the total work performance rate via ATP utilization. The energy that is consumed with food converts into heat and work after metabolization. Energy is allocated to generate heat and perform work. Work performance can explain as the capacity of a system to do useful work. Work performance is divided into internal and external work performance. Internal work performance defines unobservable muscle work such as the heart pumping, breathing, digestion process, muscle contraction and relaxing, and sending and receiving chemical and electrical signals throughout the body. External work performance implies the part of observable muscle work such as running, cycling, and movement of body parts [183,185].

Total heat loss ($\bar{Q}_{total}$) from the skin and through respiration was calculated from Equations (3.2) and (3.9) with the conversion rate recommended by Hall [186] and presented in Table 3.1.

$$\bar{Q}_{total} = 3\dot{W}_{ATP} \tag{3.9}$$

Table 3.1. Thermodynamic properties of the chemicals (adapted from Kuddusi [77])

Enthalpies of glucose, O_2 ,CO_2, and H_2O at 1 atm			
chemical	$\bar{h}_f^{\circ}$ **[kJ/kmol]**	$\bar{h}_{298K}$ **[kJ/kmol]**	$\bar{h}_{310K}^{\circ}$ **[kJ/kmol]**
$C_6H_{12}O_6$	-1260 x 10^3	-	-
$C_{16}H_{32}O_2$	-835x10^3	-	-
$C_{4.57}H_{9.03}N_{1.27}O_{2.25}S_{0.046}$	-385x10^3	-	-
O_2	0	8682	9030
H_2O	-241820	9904	10302
CO_2,	-393520	9364	9807
N_2	0	8669	9014

Entropies of glucose, O_2, CO_2 and H_2O at 1 atm	
chemical	$\bar{s}_i$
$C_6H_{12}O_6$ [298K]	212
O_2 [298K]	218.02
H_2O [310K]	215.5
CO_2 [310K]	240.4

Entropies of palmitic acid, O_2, CO_2 and H_2O at 1 atm	
chemical	$\bar{s}_i$
$C_{16}H_{32}O_2$ [298K]	452.4
O_2 [298K]	218.02
H_2O [310K]	218.29
CO_2 [310K]	243.19

Entropies of the average of 20 aa, O_2, CO_2, H_2O, and N_2 at 1 atm	
chemical	$\bar{s}_i$
$C_{4.57}H_{9.03}N_{1.27}O_{2.25}S_{0.046}$ [298K]	1.401x119
O_2 [298K]	218.02
O_2 [310K]	219.68
H_2O [310K]	218.86
CO_2 [310K]	243.64
N_2 [310K]	193.66

3.2. THERMODYNAMIC ASSESSMENT OF THE EFFECT OF GUT MICROBIOTA ALTERATIONS DEPENDENT ON THE DIET ON HUMAN

Raw data adapted from Jumpertz *et al.* [187] are used for making the thermodynamic analyses. Basic biological characteristics of the lean and obese subjects are calculated with Equations (3.10)-(3.16) [188,189] and presented in Table 3.2, where BMR represents the basal (resting) metabolic rate, *FM* and *FFM* are the fat and the free fat mass, respectively; *%FFM* is the percentage of free fat mass, *Ht* is the height and *Wt* is the weight of the subject.

$$\% \, FFM = 100 - [\% \text{ body fat}] \tag{3.10}$$

$$FM = [\text{Body weight, kg}] \, [\% \text{ body fat}] \, [0.01] \tag{3.11}$$

$$FFM = [\text{Body weight, kg}][\%FFM] \; [0.01] \tag{3.12}$$

Basal metabolic rate is calculated with four different methods, such as:

Harris-Benedict method

$$BMR = 66.4 + [(13.75) \, Wt] + [(5) \, (Ht)] - [(6.8) \, (Age)] \tag{3.13}$$

Schofield method

$$BMR = [(15.07) \, (Wt)] + 692.8 \tag{3.14}$$

Cunningham method

$$BMR = [(21.6) \, (FFM)] + 370 \tag{3.15}$$

Mifflin St. Jeor

$$BMR = [10 \times Wt] + [6.25 \times Ht] - [5 \times Age] + 5 \tag{3.16}$$

Table 3.2. Biological characteristics of the lean and the obese subjects

	Lean Subjects	**Obese Subjects**
Age (y)	32.8	35.8
Weight (kg)	73.6	121.5
Height (m)	1.77	1.73
BMI (kg/m^2)	23.4	40.4
Body Fat (%)	17.7	37.6
Weight -maintaining nutrient intake (kJ)	11,169	13,071
%FFM	82.3	62.4
FM (kg)	13.0	45.7
FFM (kg)	60.6	75.8
BMR as calculated with Harris-Benedict method (kJ/day)	7,282	9,865
BMR as calculated with Schofield method (kJ/day)	7,532	10,546
BMR as calculated with Cunningham method (kJ/day)	7,014	8,389
BMR as calculated with Mifflin-St Jeor method (kJ/day)	7,043	8,883
Average BMR of four formulas (kJ/day)	7,219	9,422

3.2.1. Mass, Energy and Entropy Balance For Human and Microbiota Subsystem

Amounts of the digested macronutrients and water intake with 10,032 and 14,212 kJ/day, i.e., 2,400 and 3,400 kcal/day, diets are presented in Table 3.3.

Table 3.3. Amounts of the digested macronutrients and water intake with 10,032 and 14,212 kJ/day diets

	10,032 kJ/day diet			**14,212 kJ/day diet**		
	Day-1	Day- 2	Day- 3	Day-1	Day- 2	Day- 3
Water (g/d)	2,000	2,000	2,000	2,000	2,000	2,000
Protein (g/d)	102	131	114	152	158	164
Fat (g/d)	79	78	78	108	110	109
Carbohydrate (g/d)	312	294	297	430	420	415

The metabolism of carbohydrates is modelled in terms of that of glucose (Equation (3.4)). Metabolism of lipids is modelled in terms of that of palmitic acid (Equation (3.5)) and that of the proteins is modelled by employing the average of 20 amino acids (Equation (3.6)). A typical person was assumed to be digesting 92% of the proteins, 95% of the fats and 99% of the carbohydrates.

The amount of the urea was calculated after considering its physiological limits as 20 g/L in the urine and 65% of it is excreted; excretion of the faeces was calculated with Equation (3.1).

Three-day averages of the amounts of the inhaled O_2, excreted CO_2, H_2O and faeces, urine and metabolic heat generation, work performance and the total heat loss from the body with 10,032 and 14,212 kJ/day diets are presented in Table 3.4.

Table 3.4. Three-day averages of the amounts of the inhaled O_2, excreted CO_2, H2O and faeces, urine and metabolic heat generation, work performance and the total heat loss from the body with 10,032 and 14,212 kJ/day diets.

	10,032 kJ/day diet	**14,212 kJ/day diet**
O_2 (g/d)	694±11	964±1
H_2O (g/d)	325±3	453±1
CO_2 (g/d)	824±10	1,147±3
Feces (g/d)	911±70	454±73
Urine (g/d)	1,125±73	1,598±75
Metabolic heat generation (kJ/day)	9,392±36	13,237±14
Work performance (kJ/day)	2,629±46	3,685±23
Heat loss (kJ/day)	7,887±139	11,055±69

Energy balance calculation was performed based on the above Equations ((3.2), (3.7)-(3.9)). Total heat loss from the skin and respiration was calculated with Equations (3.8) and (3.9)[186] by assuming steady-state conditions from Equation (3.2).

The entropy generation rate of a healthy human was calculated for each diet with Equation (3.3). Energy harvested by gut microbiota described the energy of the nutrients utilized by the gut microbiota and not returned to the host. Actually, the gut microbiota takes larger amounts of nutrients, employs them in their metabolism, and then services to the host, as described in Figure 2.2.

The daily carbohydrate, fat and protein intake given in Table 3.3 are used to calculate the amounts of the inhaled O_2, exhaled CO_2 and the extracted H_2O and faeces and urine for both the lean and the obese subjects as presented in Table 3.4.

3.2.2. Statistical Analysis

The data used in this part of the study were obtained from another published research and there were only average data representing all subjects. Therefore, we were not able to perform statistical analysis for the results of the study.

3.3. EFFECTS OF THE EXERCISE TYPES AND ENTROPY GENERATION ON ATHLETE LONGEVITY

3.3.1. Menu Planning For the Athletes

The energy needs of the athletes vary widely, depending on activity. For instance, it not uncommon for Tour de France cyclists to require more than 5,000 kcal/day. The recent guideline suggests that women need approximately 1,800-2,200 kcal/day and men need approximately 2,400-3,000 kcal/day [190]. Energy expenditure is affected by the body composition and duration, intensity and frequency of exercise [191]. Approximately 2,000 kcal/day of calories is needed by the general public, an additional 1,100 kcal/day is needed by a runner, endurance athletes usually require more calories than weight lifters [191]. In the

present study, diets were planned to provide 3,000-3,500 kcal/day for an exercise day (as seen in Table 3.5). We also assumed that when an athlete reaches a certain age, because of the lack of intense exercise he/she starts to eat as recommended for healthy individuals, i.e., 19-59 years old adults consume 1,600-3,000 kcal/day [192]. Data employed in this study were openly available for use and adapted from the references providing dietary recommendations, by citing the source. We provided the restrictions, which apply to our calculations by making some assumptions. Lifespan is indeed a long time, and there will be inevitably some changes in the nutritional preferences of the athletes in this period. We believe that after the publication of this study, many other people will utilize the same method in their research; therefore, we wanted to provide as much detail to them as possible.

There is an ideal weight and height range for athletes to be successful in any sport. Wenzel Coaching [193] indicated that the height range of the cyclist is 157-193 cm, the weight range of the male climbers is between 50 -69 kg, and those of the male sprinters are 60-90 kg. The average height and weight of these athletes were 1.80 m and 68.8 kg, in the present study calculations are performed for an athlete with a 67 kg body weight (Table 3.5). Wilk's Score measures the strength in powerlifting against other powerlifters. A weightlifter with 90 kg of body weight with Wilk's score of 450 and 500 can compete in the national-level meet or at world-class, respectively [194] calculations presented in Table 3.5 are valid for such a weightlifter. In the 2012/2013 season, the height and weight of the athletes of New Zealand's Blues rugby team were varying between 202 – 178 cm, and 80 – 129 kg, respectively [195]. In Table 3.5, assessments have been done for an average-weight rugby player.

People with varying heights and weights may be professional golfers. Irish golfer Rory McIlroy was a good PGA Tour golfer in 2010 and rose to No. 1 in the world by 2012, he was 178 cm tall and 73 kg. Tiger Woods was 188 cm tall and 70 kg when he turned pro in 1996.

He is widely regarded as one of the greatest golfers of all time and one of the most famous athletes in history and elected to the World Golf Hall of Fame in 2020. Gary Woodland was voted the most athletic golfer on the PGA tour in 2011. He was 185 cm tall and 91 kg [196]. The golfer, for whom the calculations are performed in Table 2 had exactly the same body weight as Tiger Woods and a similar body weight as Rory McIlroy.

Table 3.5. Total calories and composition of the diet plan for different groups of athletes and a 50 years old healthy retired person. Total calorific uptake, carbohydrate, protein and fat supplied by the diet to the athletes are expressed per kg of the body weight of the athletes

	Cyclist	Weightlifter	Rugby player	Golfer	50 years old healthy retired person
Body weight of the athlete (kg)	67	90	105	70	
Total caloric uptake (kcal/kg day)	52.23	41.11	38.10	32.14	2,000
Carbohydrate (g/kg day)	7.40	5.68	4.60	4.77	280
Protein (g/kg day)	2.91	2.42	2.40	1.69	77
Fat (g/kg day)	1.22	1.03	1.17	0.71	66
Total carbohydrate, protein and fat (g/kg)	11.5	9.13	8.17	7.17	423

3.3.2. Thermodynamic Consideration For Athletes' Body

Figure 3.1 illustrates the athlete's body as a thermodynamically open system. While calculating the entropy generation by the athletes the same procedure is employed as Öngel, *et al*. [182] a healthy person was assumed to digest 99% of the carbohydrates, 95% of the lipids and 92% of the proteins. Thermodynamic calculations were performed during the metabolism of carbohydrates, lipids, and proteins in terms of glucose, palmitic acid, and the average of 20 amino acids based on Equations (3.1)-(3.9).

Metabolic waste after digestion and absorption processes was removed with the urine and the faeces. Following the same procedure as Öngel *et al*. [182], the amount of urine was determined to limit its urea content to 20 g/L and 65% of urea is excreted. The amount of faeces excretion was calculated by Equation (3.1). It was assumed that athletes consume 3.0 L of per day water and non-athlete healthy people drink 2.0 L of water daily.

The amounts of the inhaled O_2, excreted CO_2, H_2O, and wastes excreted from the body for each athlete are shown in Table 3.6

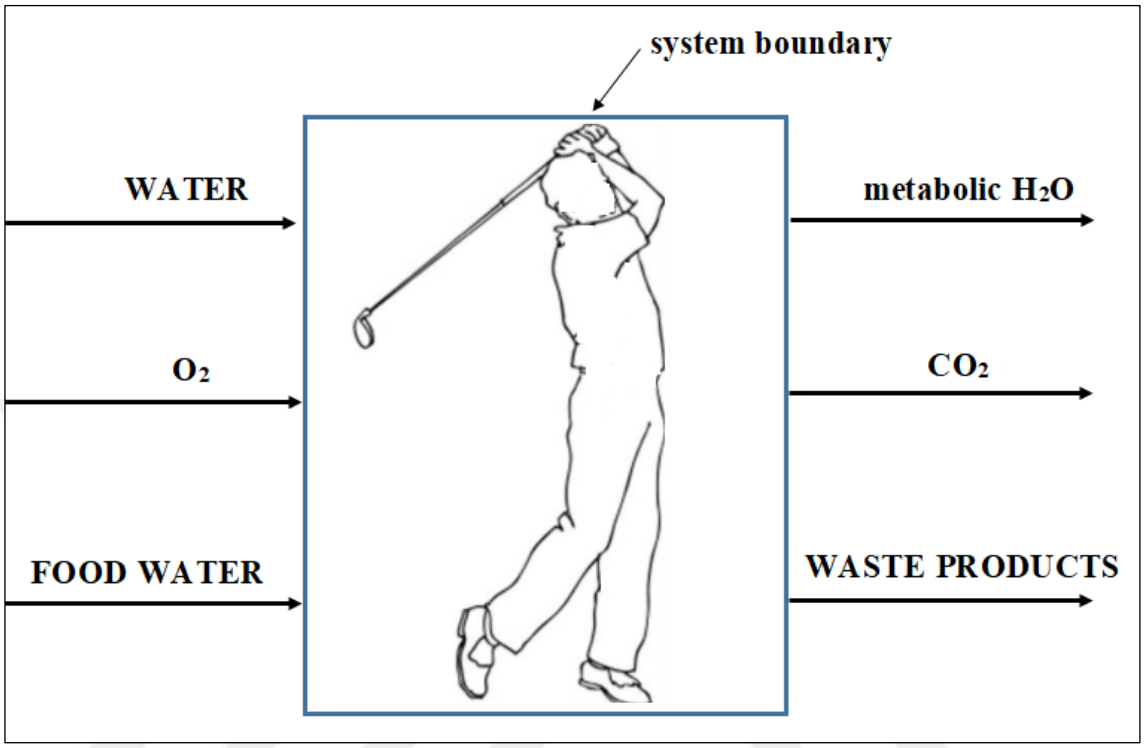

Figure 3.1. Description of the human body as a thermodynamically open system

By assuming that the nutrient intake into the body is at 25°C, and H_2O and CO_2 exit at 37 °C, energy balance was calculated via Equations (3.2), (3.4)-(3.9).

Table 3.6. The amounts of the inhaled O_2, excreted CO_2 and H_2O, urine and faces and metabolic heat production, work performance and the total heat loss from the body during the active years and after retirement.

	Cyclist	Weightlifter	Rugby player	Golfer	After retirement
O_2 (g/d)	977	1,050	1,142	628	566
H_2O (g/d)	470	501	532	305	272
CO_2 (g/d)	1,195	1,277	1,360	774	682
Faeces (g/d)	1228	1,019	709	1,972	1,303
Urine (g/d)	1,856	2,075	15,885	1,080	733
Metabolic heat production (kJ/day)	13,549	14,584	9,428	8,686	7,691
Work performance (kJ/day)	3,709	3,950	3,716	2,413	2,247
Heat loss (kJ/day)	11,126	11,850	11,147	7,238	6,740

According to the literature descriptions, the weights of a male cyclist, weightlifter, rugby player and golfer were assumed 67, 85, 105 and 70 kg, respectively. The entropy generation rate of the athletes was calculated depending on their diets by Equation (3.3).

The athletes were assumed to retire when they become 50 years old, and start consuming a special diet prepared for them. The lifespan entropy generation limit was assumed to be 11,404 kJ/K kg [48,75] and the athletes die when they come to this limit. Diet plans have been designed in the present study by referring to the nutritional guidelines and scientific articles to provide sufficient nutrients for each athlete, and then the life span entropy has been calculated. These calculated lifespans are then compared to the observed longevities to be sure that the thermodynamic model is correct.

3.3.3. Statistical Analysis

The data used in this part of the study were obtained from another published research and there were no data of all subjects. Therefore, we were not able to perform statistical analysis for the results of the study.

3.4. ASSESSMENT OF ENTROPY GENERATION IN HUMAN SUBJECTS WHEN EXPOSED TO LOW ENERGY AVAILABILITY AND VARYING PROTEIN INTAKE

This study was designed to evaluate athletes' bodies in terms of thermodynamics depending on their diet and exercise intensity by using the data of Murphy *et. al* [197]. In this study, data from seven, young healthy, endurance-trained men were used. The characteristics of the subjects are presented in Table 3.7.

Table 3.7. Physiological characteristics of the athletes

Age (y)	23.85 ± 4.09
Height (cm)	181.50 ± 9.49
Weight (kg)	86.87 ± 7.56
FM (kg)	15.19 ± 3.10
FFM (kg)	69.53 ± 7.63

The subjects consumed three different types of diets during the experiments in a randomized order: The control diet (CON) provided 230.12 kJ/kg FFM/day and a protein intake of 1.7 g/kg/day. In the two intervention diets, which resulted in LEA, dietary energy intake was restricted to 125.52 kJ/kg FFM/day, once with a low protein intake (0.8 g/kg/d; LEA-LP) and once with a high protein intake (1.7 g/kg/d; LEA-HP). During all conditions, participants exercise to expend 62.76 kJ/kg FFM/day, resulting in energy availability of 167.36 kJ/kg FFM/day (CON) or 62.76 kJ/kg FFM/day (LEA). In this study, we reduced energy availability to 62.76 kJ/kg FFM/day based on the previous research]showing that 5 days of EA ≤ 125.52 kJ/kg FFM/day energy availability caused negative changes in endocrine and metabolic responses and the uncoupling of bone in reactive young women [167,198]

3.4.1. Thermodynamic Assessment of The System Dependent on The Diets

To support metabolism, sustain and keep alive the body, which is an open thermodynamic system that is not in equilibrium, requires a continuous supply of energy along the boundary of a living system [199]. This vital energy is supplied to the body through food. Equations (3.4)-(3.6) belong to the chemical reaction of oxidation of the macronutrients, which is the catabolism event. Figure 1 shows an athlete's body as a thermodynamically open system. Table 3.8 presents individuals' macronutrient intake, oxygen consumption, and carbon dioxide production rates for each diet. The substrate oxidation rates were determined via Equations (3.17)-(3.19) to perform thermodynamic calculations. Then a macronutrient balance was determined.

$$FOx[g/min] = 1.67VO_2[L/min] - 1.67VCO_2[L/min] - 0.307POx \quad (3.17)$$

$$CHOx[g/min] = 4.55VCO_2[L/min] - 3.21VO_2[L/min] + 0.459POx \quad (3.18)$$

$$POx[g/min] = [RMR\ [kj/min] \times 0.15] / 16.74\ (kJ) \quad (3.19)$$

Where it was assumed that 15% of RMR is provided by the oxidation of protein [200]. In the equations, VO_2 represents the oxygen consumption rate and VCO_2 defines the carbon dioxide production rate.

Table 3.8. Daily macronutrient intake, oxygen consumption and carbon dioxide production rate

	PROTEIN (g/d)	CARBOHYDRATE (g/d)	FAT (g/d)	VO_2 [L/d]	VCO_2 [L/d]
CONTROL	147.0 ± 12.9	612.8 ± 87.9	111.9 ± 11.2	721.4 ± 79.7	631.2 ± 80.2
LEA-LP	69.2 ± 6.1	345.1 ± 48.6	58.5 ± 5.2	704.3 ± 82.6	557.1 ± 72.5
LEA-HP	135.6 ± 31.3	280.0 ± 29.4	27.3 ± 5.3	731.3 ± 105.0	611.4 ± 74.3

Metabolic heat generation, work performance and total heat loss calculations were performed by using Equations (3.2), (3.4)-(3.9).

Total energy expenditure includes resting metabolic rate (RMR), non-exercise activity thermogenesis (NEAT), dietary-induced thermogenesis (DIT), and exercise energy expenditure (EEE). The RMR of each athlete was measured using indirect calorimetry. The NEAT value was determined by a wrist-worn triaxial accelerometer and indirect calorimetry was used to measure EEE. Energy balance and energy availability for each diet were calculated by using the data in Table 3.9. Here, it was assumed that DIT equals 10% of EI.

Table 3.9. Energy intake, resting metabolic rate, and exercise energy expenditure

	EI (kJ/d)	RMR (kJ/d)	NEAT (kJ/d)	DIT (kJ/d)	EE (kJ/d)
CON	16592.5 ± 1846.4	7702.3 ± 889.1	1764.8 ± 786.6	1659.4 ± 184.5	4768.5 ± 661.9
LEA-LP	9041.0 ± 1007.9	7224.5 ± 658.1	1839.3 ± 937.6	905.0 ± 100.8	4611.6 ± 1866.1
LEA-HP	9050.0 ± 1007.9	7274.7 ± 1180.3	2794.5 ± 2243.0	905.0 ± 100.8	4773.5 ± 828.4

In this part, it was assumed that athletes consumed these diets throughout their lifespans. Entropy generation and accumulation calculations are performed based on this assumption. The entropy generation rate due to the oxidation of macronutrients was calculated by using Equation (3.3).

According to Ulu *et al.* [174], storage of glycogen and lipid cause negligible entropy generation while glycogen and lipid reuse lead to entropy generation. Entropy generation due to glycogen and lipid reuse was found by Equation (3.21).

$$S_{gen} = [Amount\ of\ glycogen\ reuse]\ [1.25\ kJ/Kmol]\ [1\ mol/180\ g] + [Amount\ of\ lipid\ reuse]\ [1.93\ kJ/Kmol]\ [1\ mol/256\ g] \quad (3.20)$$

The entropy exportation rate was calculated by assuming that 5.8% of energy intake was lost in faeces, 4.5% of energy intake was lost in the urine, and 0.4% of energy intake was exported as methane Equation (3.21) [201].

$$Entropy\ exportation = [[EI \times 0.058] + [EI \times 0.045] + [EI \times 0.004] + \ ]/T \quad (3.21)$$

The entropy accumulation rate was determined by subtracting entropy exportation from entropy generation (Equation (3.22)).

$$Entropy\ accumulation = Entropy\ generation - Entropy\ exportation\ rate \quad (3.22)$$

The lifespan entropy generation limit was assumed 11,404 kJ/K kg, and the lifespan was estimated performed for each athlete [48,75]. To predict the effects of diets on lifespan, the

calculations were performed for three different situations. In the first condition, it was assumed that athletes consumed all diets throughout their lifespans. For the second and third states, it was considered that athletes followed the CR diets for 5 and 10 years, then, continued the CON diet until their 50 (retirement) and after retirement, followed the new diet [prepared by Yildiz *et al*., 2022 [177].

3.4.2. Statistical Analysis

All statistical analyses were performed by SPSS software 28.0 (IBM, New York, USA) Version Descriptive statistics involves a comparison of entropy generation rate and lifespan estimation among three different diets. Based on the distribution of the data, differences among the diets in terms of macronutrient oxidation, work performance, entropy generation and lifespan estimation were tested by Kruskal-Wallis [202]. In the current study, the p-value < 0.05 represents statistical significance.

4. RESULTS AND DISCUSSIONS

4.1. THE EFFECTS OF GUT MICROBIOTA ALTERATION ON ENERGY BALANCE

Tükenmez *et al*. [203], while studying mixed-culture multi-product fermentation of cellulose fibres with rumen microorganisms, reported that when a fermentation medium was disturbed, some of the microorganisms did not grow, while some others did and the fermentation products changed accordingly. Gut microbiota is a mixed culture, multi-product system subject to similar changes as those of the rumen microorganisms upon disturbance. Medical drugs used by the patients may disturb the gut microorganisms; as a result, both the products of the gut microbiota and their interaction with the host may change. It has been known that SCFAs and other gut microbiota metabolites play a role in the regulation of the energy available to the host [89,129]. Table 4.1 shows that, on a 10,032 kJ/day diet, the relative increase in *Firmicutes was* almost the same both with the lean and the obese subjects, i.e., 1.3 and 1.4%, respectively. On this diet, energy harvested by the gut microbiota in three days was 40 kJ with the lean and 45 kJ with the obese subjects, respectively. On a 10,032 kJ/day diet, entropy generation with the contribution of the gut microbiota was 4.9×10^{-7} kW/kg_{body} K with the lean and 5.6×10^{-6} kW/kg_{body} K with the obese subjects. With the obese subjects, both the energy harvested and the entropy generation with the contribution of the gut microbiota was 1.1 times of those of the lean subjects. On a 14,212 kJ/day diet, a relative abundance of the *Firmicutes* increased by 8.4% for lean and 1.7% for obese subjects, and the energy harvested by the gut microbiota in three days was 2623 kJ/day by the lean subjects, while it was 54 kJ with the obese subjects. On a 14,212 kJ/day diet, in parallel with the higher energy harvest, entropy generation with the contribution of the gut microbiota was 3.3×10^{-6} kW/kg_{body} K with the lean and 6.9×10^{-7} kW/kg_{body} K with the obese subjects.

Table 4.1. Energy loss with faeces and urine and the total entropy generation rate by 73.6 kg lean and 121.5 kg obese subjects on 10,032 and 14,212 kJ/day diets and energy harvest and entropy generation rates by the gut microbiota

	10,032 kJ/day diet		**14,212 kJ/day diet**	
	lean subjects	obese subjects	lean subjects	obese subjects
Relative increase in *Firmicutes*	1.3%	1.4%	8.4%	1.7%
Energy excretion with the feces (kJ/day)	560	556	606	727
Energy excretion in the urine (kJ/day)	368	414	443	472
Total entropy generation rate with the metabolism of the subjects [kW/kg_{body} K]	$4.00x10^{-6} \pm 0.03x10^{-6}$	$2.42x10^{-6} \pm 0.02x\ 10^{-6}$	$5.64x10^{-6} \pm 0.01x10^{-6}$	$3.41x10^{-6} \pm 0.01x\ 10^{-6}$
Energy harvested by the gut microbiota in three days (kJ)	40	45	263	54
Increase in the entropy generation rate with the contribution of the gut microbiota [kW/kg_{body} K]	$4.9\ x10^{-7}$	$5.6\ x\ 10^{-7}$	$3.3\ x\ 10^{-6}$	$6.9\ x\ 10^{-7}$

Figure 4.1 represents the allocation of energy of the nutrients by the human superorganism to the host, faeces, urine and the gut microbiota during consumption of a 10,032 kJ/day and a 14,212 kJ/day diet. When we consider the average BMR estimate, we see that the 10,032 kJ/day diet provided 28% more energy than the average BMR of the lean subjects, and 6% less energy than the average BMR estimate of the obese subjects. On the other hand, the 14,212 kJ/day diet is almost double of the BMR of the lean and almost three times the BMR of the obese subjects. With the lean subjects, energy harvested by the gut microbiota was 5.3

times that of the obese subjects, while the entropy generation by the microbiota of the lean subjects was 4.8 times of that of the obese subjects. These results imply that, when the subjects are provided with less caloric intake, they prefer to use a larger fraction of it in metabolism and generate more entropy, however, when they are provided with an abundance of calories we observe a totally different case and most probably calories coming from the food are stored in the adipose tissue of the host.

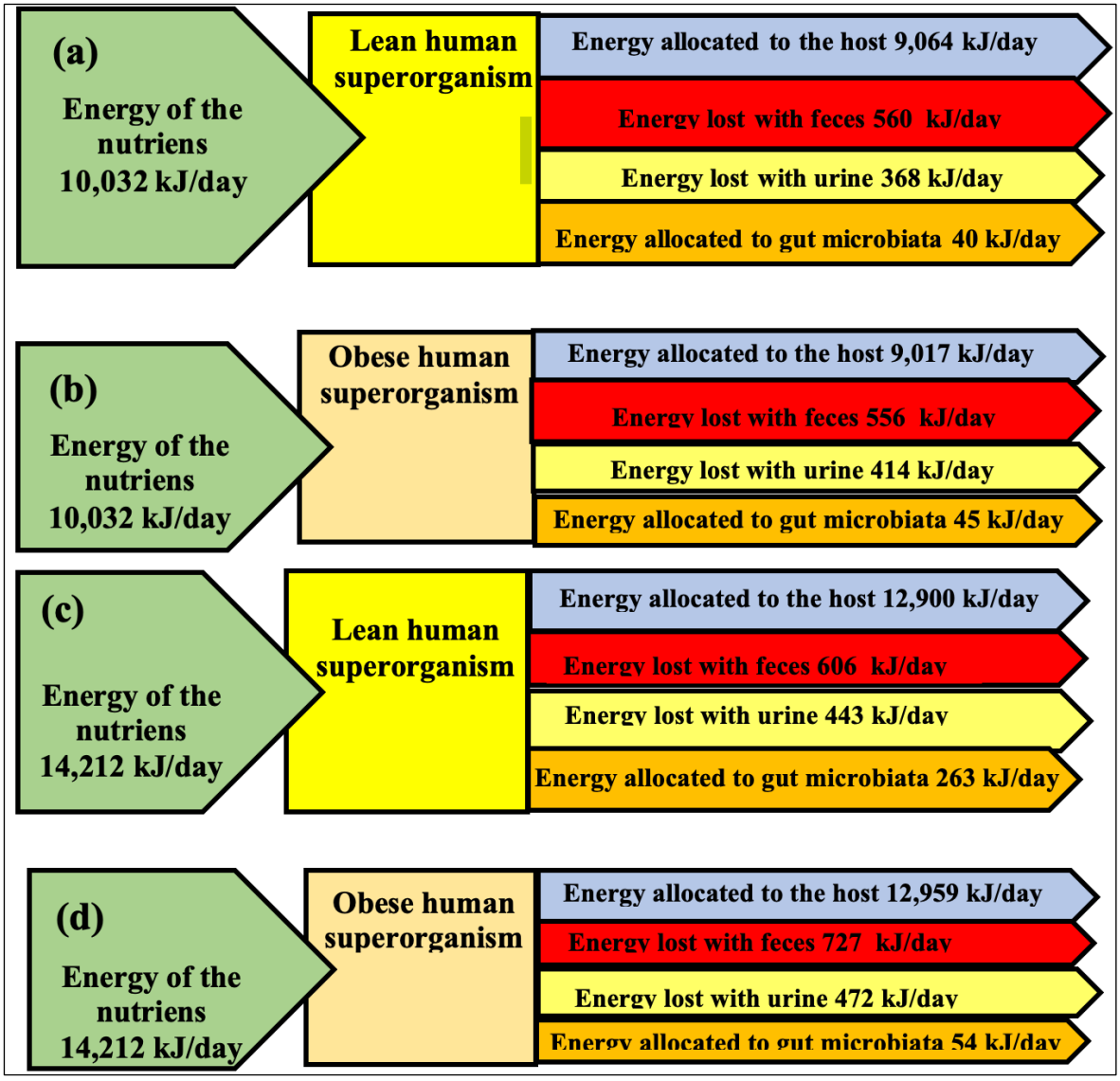

Figure 4.1. Schematic description of the allocation of the energy of the nutrients to host, faeces, urine and the gut microbiota (a) by the lean human super organism with 10,0332 kJ/day of food supply, (b) by the obese human super organism with 10,0332 kJ/day of food supply, (c) by the lean human super organism with 14,212 kJ/day of food supply, (d) by the obese human super organism with 14,212 kJ/day of food supply

According to Jumpertz *et al.* [187], a 20% increase in *Firmicutes* was accompanied by nearly 627 kJ of increase in the energy harvested from the nutrients, while a 20% increase in *Bacteriodetes* was accompanied by about 627 kJ of decrease. The data presented in Table 4.1 and Figure 4.1 shows that the energy harvested by both lean and obese subjects on a 10,032 kJ/day diet was lower when compared to that of the weight-maintaining diet data. The average amount of faeces on the 10,032 kJ/day diet was 50% higher than that of the 14,212 kJ/day diet since protein consumption was 27% higher with 14,212 kJ/day diet (see Table 4.2), and the higher amounts of protein consumption caused to higher amounts of urea production and urine extraction on 14,212 kJ/day diet. The average amount of urine excreted with a 14,212 kJ/day diet was 30% higher than that of a 10,032 kJ/day diet.

4.1.1. Contribution of the gut microbiota to BMR

In the literature [188,189] each of the estimates of the BMR with the Harris-Benedict, Schofield, Cunningham and Mifflin-St Jeor methods was found satisfactory in certain cases; and unsatisfactory in others; therefore, it would not be possible to expect any of them to be consistently better than the others; consequently, all of them were used together in the present study. If the relative abundance of *Bacteroides* increases in the gut microbiota, instead of *Firmicutes,* energy expenditure does not change much whether the lean subjects are on 10,032 or 14,212 kJ/day diets (Table 3.2). When estimated with the Harris-Benedict equation, the BMR of the obese subjects increases by 2.66% and 0.55% on 10,032 and 14,212 kJ/day diets, respectively. However, with the Cunningham equation, we calculated 0.57% and 0.64% increase in BMR for the lean subjects, on 10,032 and 14,212 kJ/day diets, respectively; BMR of the obese subjects increased by 3.13% and 0.64% on 10,032 and 14,212 kJ/day diets, respectively. With the Mifflin-St. Jeor equation, BMR of the lean subjects on 10,032 kJ/day of energy intake, the difference between energy intake and resting energy expenditure was the highest, 2,999 kJ/day.

Table 3.4 presents the daily estimates of heat generation, work performance and the total heat loss from the body with 10,032 and 14,212 kJ/day diets. External work performance potential was higher during the consumption of a 14,212 kJ/day diet in both lean and obese subject groups. The amounts of the heat losses were calculated as three times of the mechanical work performance. When we use the average of the three days for comparison,

we see that the difference between the metabolic heat generation rates and heat loss rates via respiration and perspiration were 6,291 and 2,182 kJ/day during consumption of 10,032 and 14,212 kJ/day diets, respectively.

4.1.2. Effects of Diet-Related Gut Microbiota Alteration on Entropy Generation

An ecosystem develops progressively if it can export entropy at a higher than its generation [204]. The gut microbiota is a highly complicated ecosystem, in addition to the interaction of the microbiota among themselves, they also interact with the host [205,206]. The gut microbiota ecosystem, like other ecosystems, maintains its presence far from the thermodynamic equilibrium. In this study, we calculated the entropy generation rate of the two subject groups based on the two diets for three days (as shown in Table 4.1) and found that the entropy generation rate of the subjects increased with the contribution of the gut microbiota. Energy harvested by the gut microbiota causes an additional entropy generation rate increment in the human superorganism. Entropy generation rates by the lean subjects were 39.4% higher than those of the obese subjects on a 10,032 kJ/day diet; entropy generation rates by the lean subjects were 13.2% higher than those of the obese subjects on a 14,212 kJ/day diet (Table 4.1 and Figure 4.2). Details of the entropy generation rates by the lean host and the gut microbiota when the human superorganism is provided with 10,332 kJ/day of food are described in Figure 4.3, where it is observed that 22% of the total entropy generation is exported by the gut microbiota, for the specified food intake.

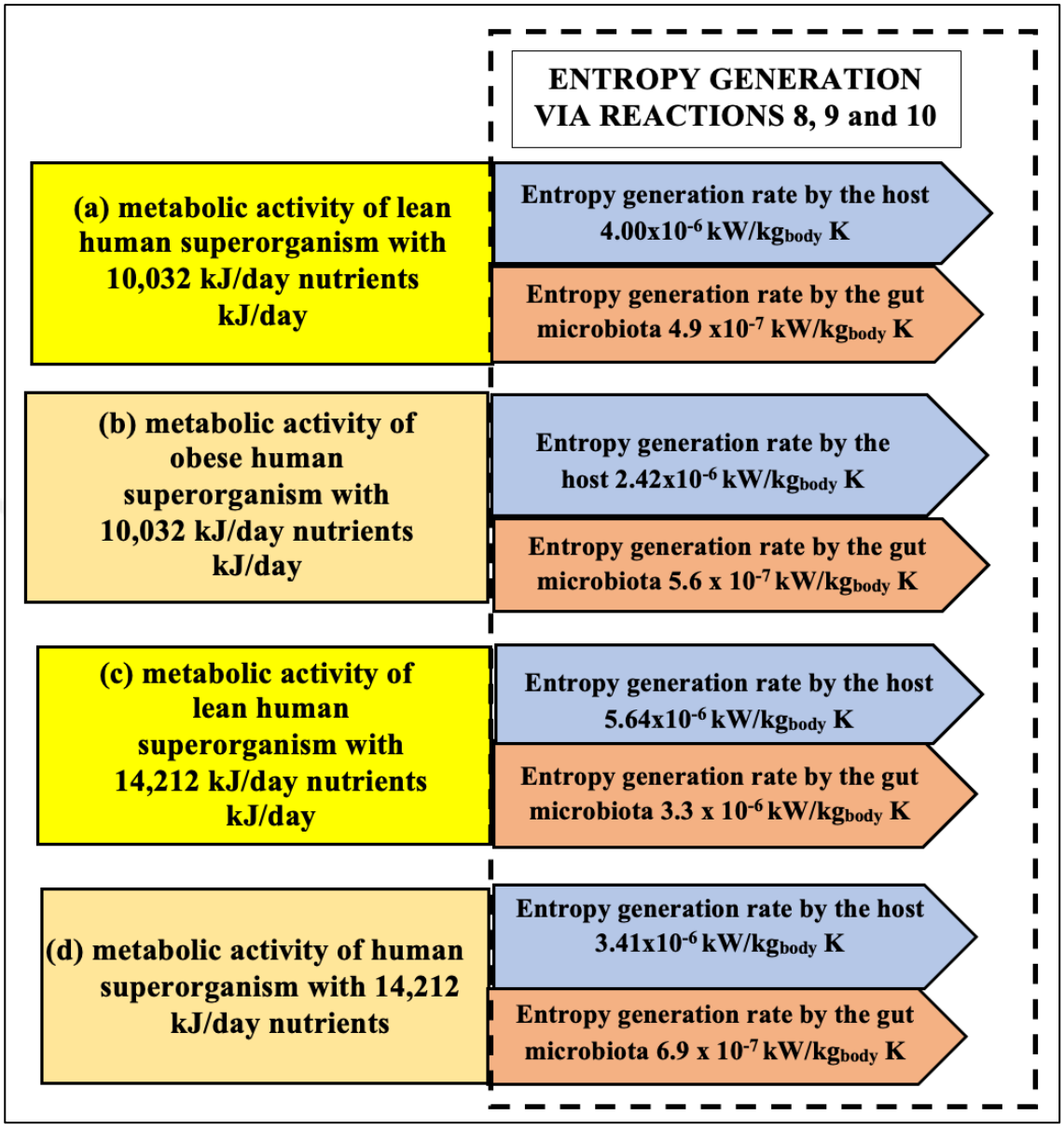

Figure 4.2. Schematic description of entropy generation rates by the hosts and the gut microbiota (a) by the lean human super organism with 10,332 kJ/day of food supply, (b) by the obese human super organism with 10,332 kJ/day of food supply, (c) by the lean human super organism with 14,212 kJ/day of food supply, (d) by the obese human super organism with 14,212 kJ/day of food supply

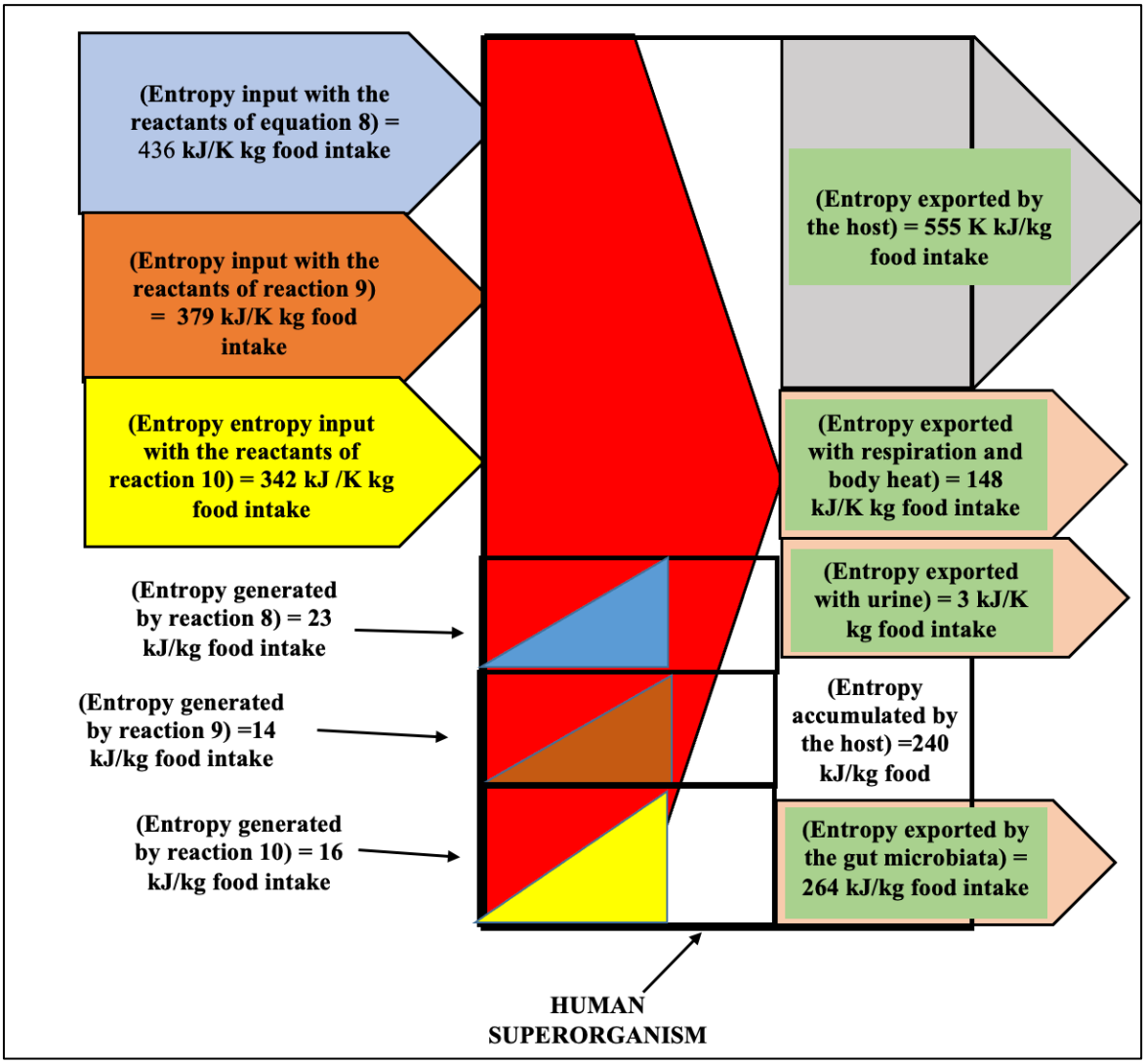

Figure 4.3. Details of the entropy generation rates by the lean host and the gut microbiota when the human superorganism is provided with 10,332 kJ/day of food

4.1.3. Energy Harvesting and Entropy Generation via Gut Microbiota

Living organisms must maintain a state of high organization [2], where entropy accumulation implies increasing disorder or structural impairment [70]. Metabolic heat generation changes the energy states of the biomolecules and renders them inactive or malfunctioning [64]. While people are young, genetically induced repair and replacement processes are capable of maintaining the balance in favour of the functioning molecules, but with ageing, the balance between these processes tends toward inactivation and malfunctioning [65]. Following exactly the same behaviour as the other dissipative systems,

energy is needed to prevent entropy accumulation, e.g., to heal the cumulative damage in the organisms [1]. As explained by Yalcinkaya *et al.* [74] with the decline of mitochondrial energy generation, organisms start experiencing structural impairment. Living things have a strong tendency to approach equilibrium even when they are far from equilibrium structures, which indicates ageing and rising entropy. Living things need to build an entropy gradient with their environment in order to thrive outside of equilibrium. An open system may deviate significantly from equilibrium since such gradients can only be sustained by using energy received from outside. The gut microbiota of the human superorganism uses the host's faeces as a means of excreting their own metabolic heat and entropy from the body without harming it. Thermodynamic analyses presented in this study prove their function as entropy-exporting agents. Lewins [207] argued that the pollutants leaving a production facility actually have higher entropy and are structurally less organized than the product itself, serving as agents to export entropy. In the present study, faeces, leaving the body establish an analogy with the pollutants leaving a production plant, and thus strengthens the hypothesis suggested here. The reason for the development of the gut microbiota as a thermodynamic sub-system within the body of the host is explained by Bejan's constructal theory; which states that "the physical structure, including geometric configuration, topology, and etc., of a system, springs out of the process of global thermodynamic optimization, subject to global constraints [208]. This principle generates structure not only in engineering, but also in physics and biology". The conclusion "*fraction of the metabolic ageing damage is flushed out by gut microbiota to extend longevity*" describes a continuous optimization occurring in nature, and is consistent with Bejan's constructal theory.

4.2. DIET-DEPENDENT ENTROPIC ASSESSMENT OF ATHLETES' LIFESPAN

In the present study, we prepared four different diets for cyclists, weightlifters, rugby players, and golfers to consume during their active sports careers and another diet was written for the retirement period of their life. Cycling is among the high-static and high-dynamic component sports (Table 2.2). Therefore, the oxygen uptake and metabolic activity of cyclists are higher than those of athletes involved in other sports such as weightlifting, rugby, and golf. The results of the present study indicate that the oxygen uptake of a cyclist would be 977 g/day and his metabolic heat generation would be 13,549 kJ/day. The results of this study suggest that a cyclist may live 56 years and generate 6.4 x 10^{-6} kW/kg K per

day and 200 kJ/kg K per year of entropy (Table 4.2) when he consumes the special diet for cyclists diet. If he should change his diet after retirement, he may live 6.4 years longer and generate 2.9 x10^{-6} kW/kg K of daily and 89.8 kJ/kg K less annual entropy [Table 4.2]. A cyclist produces the highest entropy in comparison with a weightlifter, rugby player, and golfer. This metabolic difference results from the weight difference between the athletes and different amounts of calorie intake and diet composition. Cycling has been recommended as a form of exercise for people by Martin *et al.,* [209]. Likewise, Sanchis-Gomar, *et al.* [210] discovered that whereas Tour de France competitors had an average lifetime of 81.5 years, 50% of the general population passed away at 73.5. According to our findings, bikers who engaged in high-intensity exercise had lower life spans than others because they generated more entropy at a faster pace. These results should be interpreted with caution as mental health and physiological changes were not taken into account.

Table 4.2. The total entropy generation rate and the expected lifespan of the athletes

	Cyclist	Weightlifter	Rugby player	Golfer
Daily entropy generation rate [kW/kg K] in case of consumption of the athletes' diet	6.4x10^{-6}	5.5x10^{-6}	4.8x10^{-6}	3.9x10^{-6}
Annual entropy generation rate [kJ/kg K] in case of consumption of the athletes' diet	200	170	150	122
Total entropy generation [kJ/kg K] until retirement	10,010	8,491	7,514	6,121
Lifespan [years] in case of consumption of the athletes' diet throughout the lifespan	56	66	75	92
Daily entropy generation rate [kW/kg K] in case of consumption of the retirement diet	3.5x10^{-6}	2.8x10^{-6}	2.3x10^{-6}	3.4x10^{-6}
Annual entropy generation rate [kJ/kg K] in case of consumption of the retirement diet after retiring	110	87	70	106
Lifespan [years] in case of consuming the athletes' diet for 50 years and then consuming the retirement diet	63	84	105	100

Weightlifting has high static (>50% MVC) and low dynamic (<40% Max O_2) components as shown in Table 2.2. Our results show that a weightlifter consumes 1,050 kg/day of O_2 and generates the highest amount of metabolic heat with 14,584 kJ/day during his active sports life as an athlete (Table 3.6). He generates 5.5 x10^{-6} kW/kg K day and annual 169.8 kJ/kg K year entropy; therefore if he remains on the weightlifter diet until the end of his lifespan, he may live until 66 years of age. However, if he consumes the retirement diet for the rest of his life, his remaining life expectancy may increase by 17.40 years (Table 4.2). Huebner, *et al.*[211], argue that Olympic weightlifting results in high power output; therefore, explosive power, speed and strength are necessary for it and the prevalence of metabolic disorders are low in weightlifters due to the effects of physical activity on human health. In this study, it is found that the work performance of the weightlifter is the highest with 3,950 kJ/kg per day among the four groups we studied.

Rugby sport requires 20-50% MVC and 40-70% of the Max O_2 (Table 2.2). A rugby player inhales 1,142 g/day of O_2 during his active sports life (Table 3.6). Our results indicated that, on average, a rugby player may live 105 years, this is longer than the expected average lifespan of cyclists, weightlifters, and golfers if he consumes the athletes' diet prepared for him until the age of 50, and after this age the retirement diet (Table 4.2). If he continues to consume the athlete's diet his life expectancy may decrease for 30 years and on average he may generate 4.8 x10^{-6} kW/kg K of daily and 150 kJ/kg K of annual entropy. If the rugby player should choose to uptake the same calorie and have the same-composition diet in his retirement, he may generate lower daily nutritional entropy per weight, i.e., 2.3 x 10^{-6} kW/kg K. This is less than what the average cyclist, weightlifter, and golfer generate every day in entropy. According to Davies *et al.* [212], elite professional rugby players who were 50 years or older had reduced rates of diabetes, cardiovascular disease, and hypertension, whereas their rates of anxiety and musculoskeletal disorders were greater than those of individuals in the English Longitudinal Study of Aging. This might mean that rugby players don't typically have metabolic illnesses and that stress or musculoskeletal morbidity doesn't shorten their lifespan.

As shown in Table 2.2, per cent of MaxO_2 and MVC of golf is lower than that of a cyclist, weightlifter or rugby player. According to our results, golfers consume a lower amount of oxygen, and their metabolic heat generation, work performance and heat loss via respiration and perspiration during their active life period are lower in comparison with cyclists,

weightlifters, and rugby players (Table 3.6). Our results also showed that, if the athletes consume the special diets for their active life periods during their whole life, golfers' daily entropy generation rate, i.e., 3.9 x10^{-6} kW/kg K would be lower than those of the other athletes and thus, their lifespan expectancy, 91.9 years, would be higher than those of the others (Table 4.2). If they should consume the retirement diet in their retirement years, a golfer may live for 100 years and generate 3.4 x 10^{-6} kW/kg K entropy daily (Table 4.2). Our assessment was based on the assumption that athletes changed their diet by the age of 50, but if they retired early, they could switch to their retirement diet sooner, suggesting that under certain circumstances, life may be extended. more than given in Table 4.2. According to Farahmand *et al*. [213], golfers have the lowest mortality rates due to the lower golf training intensity compared to other athletes' practices**.** Murray *et al.*[214] , suggested that golf is a moderate-intensity aerobic exercise that contributes positively to life expectancy, and that golf is beneficial to the health of older adults because it involves walking exercises. Hayflick established the entropic age concept [62–65], and Annamalai and co-workers improved it significantly [48,66,75] by working on numerical examples and estimating the ageing stress on each organ [66]. Kuddusi [77], Öngel *et al*. [182] and Patel and Rajput [215] made a further contribution to the entropic age concept by applying it to different diets. Every athlete consumes a specially designed-diet to be successful. Different longevities are given in the literature for the athletes participating in different sports. In the present study, a perfect agreement was found between the observed and the athletes'-special diet-based longevity estimates.

Our results are based on the nutritional entropy generation and do not show the exact lifespan of athletes such as rugby players, cyclists, weightlifters, and golfers, because there are also several other factors such as disease, mental condition, bodily injury and genetic factors affecting the athletes' life expectancy. In a recent study, Öngel *et al*. [216] reported how a disease may affect entropy generation in a patient's lifespan.

In his Nobel-winning study, Schrödinger [58] explains that living systems import energy and export entropy to maintain their lives. Internal and external work performance and entropy generation by the living systems are studied in detail by Semerciöz *et al.* [43,185] elaborated the entropy generation and entropy accumulation concept by the living system further. The work performance, entropy generation and accumulation concepts as discussed by these authors also apply to this study. Semerciöz *et al*. [185] refer to the work performed by the

lungs, heart, liver, kidneys, and nervous system and manufacturing of the bones and muscles are "*internal work"*. If the athlete is pregnant, work performed by her to synthesize the baby is also regarded as internal work. All the work, leading to consequences observable to the eye from the outside of the system, such as chewing, running, walking etc. is "*external work*". An athlete may perform all of these kinds of work by utilizing ATP.

4.3. ASSESSMENT OF ENTROPY GENERATION IN HUMAN SUBJECTS WHEN EXPOSED TO LOW ENERGY AVAILABILITY DIET AND VARYING PROTEIN INTAKE

4.3.1. Macronutrient Metabolism

This study was designed to determine the effect of diet types on energy balance and energy availability as well as metabolic heat production, total heat loss, and work performance. In this part of the study, the amount of calorie and macronutrient intake, body composition, and the physical characteristic of seven athletes were used to calculate the entropy generation/accumulation and lifespan. The athletes were exposed to a caloric restriction diet with low and high protein intake. Daily protein oxidation rates were 69.0 ± 8.0 g/d [95% Cl: 61.7-76.4], 64.7 ± 5.9 g/d [95% Cl: 59.3-70.2] and 65.2 ± 10.6 g/d [95% Cl: 55.4-75.0] for CON, LEA-LP, and LEA-HP, respectively. According to statistical analysis, there was no significant difference in protein oxidation rates (LEA-LP-LEA-HP: p= 0.747, LEA-LP-CON: p= 0.245, LEA-HP-CON: p= 0.401). The carbohydrate metabolism rate was higher during consumption of the CON diet (587.6 ± 308.4 g/d, 95% Cl: 302.4-872.8) when compared to LEA-LP (303.6 ± 139.9 g/d, 95% Cl: 174.1-433.0) (p=0.039). For daily fat oxidation, there was no significant difference in terms of diet (CON versus LEA-HP: p=0.389, CON versus LEA-LP: p=0.085, LEA-HP versus LEA-LP: p=0.389) (see Table B1). Figure 4.4 presents the percentage of macronutrients metabolized/oxidized by the athletes. During the LEA-LP diet, the percentage of protein oxidation rate was 94.0 ± 10.1 [95% Cl: 84.7- 103.3] and this amount was significantly higher than other diets followed (CON versus LEA-LP: p= 0.004, LEA-HP versus LEA-LP: p= 0.007). The percentage of daily carbohydrate percentage significantly increased while following the LEA-HP diet in comparison with the CON diet (p=0.048). The percentage of fat oxidation was higher during

consumption of the LEA-HP and LEA-LP diets (CON versus LEA-HP: p<0.001, CON versus LEA-LP: p=0.012).

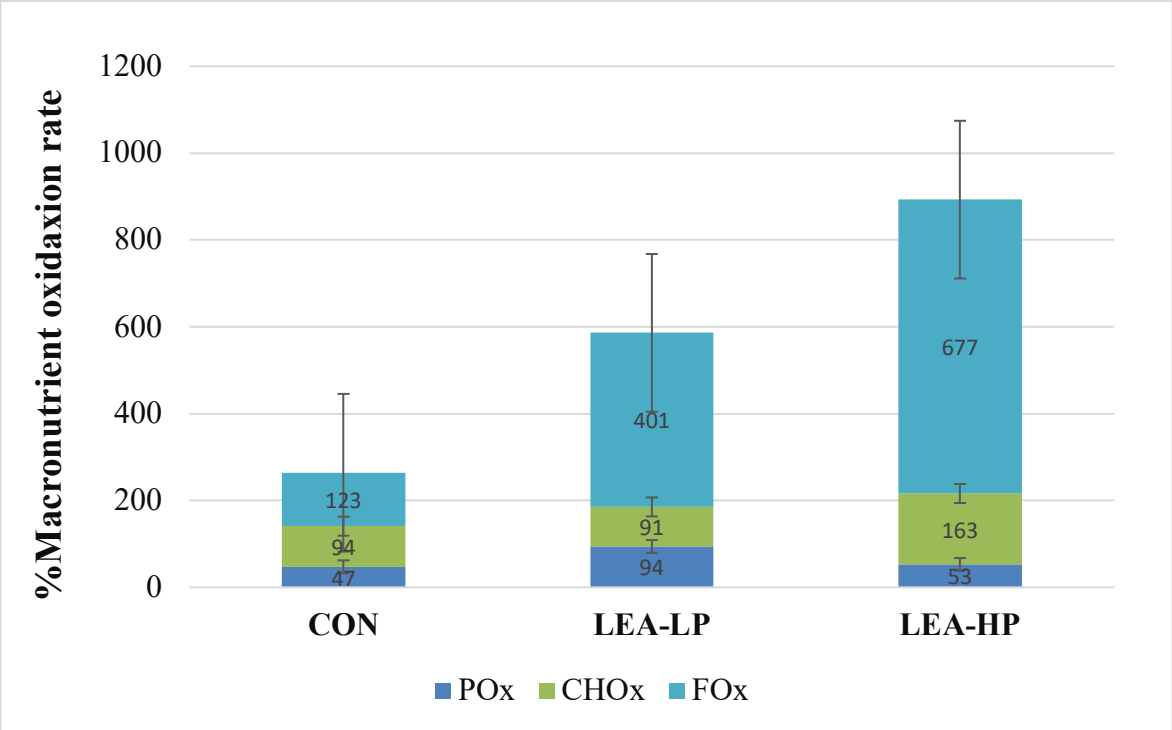

Figure 4. 4. Graph of percentage of daily macronutrient metabolization during each diet (Calculation was performed based on macronutrient intake. CON: control diet, LEA-LP: caloric restriction diet with low protein content, LEA-HP: caloric restriction diet, POx: protein oxidation, CHOx: carbohydrate oxidation, FOx: fat oxidation)

The results of this part of the study show that carbohydrate deficiency was higher during the consumption of LEA-HP when compared to the LEA-LP diet (p=0.025) while the fat deficit was a little higher in the LEA-LP diet (p=0.965). Contrary to expectations, there was a fat deficiency (-58.9 ± 86.6 g/d, 95% Cl: -139.0-21.1) during the consumption of the CON diet for three individuals (see Table 4.3).

Table 4.3. Macronutrient balance for each type of diet

	Protein balance (g/d)	Carbohydrate balance (g/d)	Fat balance (g/d)	Glycogen reuse (g/d)	Lipid reuse (g/d)
CON	69.6 ± 14.1 [95% Cl: 56.5-82.6]	16.8 ± 283.4 [95% Cl: -245. 2-278.9]	-9.3 ± 148.6 [95% Cl: -146.7-128.1]	99.48 ± 167.81 [95% Cl: -55.71-254.68]	58.88 ± 86.60 [95% Cl: -21.1-138.98]
LEA-LP	4.4 ± 7.25 [95% Cl: -2.3-11.2]	36.4 ± 116.1 [95% Cl: 36.4-116.1]	-169.1 ± 58.12 [95% Cl: -222.4+115.4]	31.39 ± 59.28 [95% Cl: -23.44-86.21]	144.95 ± 109.84 [95% Cl: 40.78-243.96]
LEA-HP	70.4 ± 36.0 [95% Cl: 37.1-103.7]	-197.4 ± 166.3 [95% Cl: -351.2+43.5]	-152.9 ± 96.8 [95% Cl: -242.4+63.4]	195.65 ± 160.37 [95% Cl: 47.32-343.97]	142.37 ± 47.72 [95% Cl: 102.39-254.27]

The macronutrient oxidation process supplies energy to the body. Our results suggested that the type of diet affects the number of macronutrients oxidized. Fat oxidation occurs to supply energy demand when glycogen depletion, down glycogenesis related to a low carbohydrate diet and fasting [217]. However, de novo lipogenesis (58.6 g/d fat production) occurred in one individual metabolism during the consumption of the CON diet. De novo lipogenesis results from the conversion of excess carbohydrates into fatty acids in healthy humans [218]. On the other hand, in this study, despite carbohydrate deficiency, the fat produced by the athlete. In this case, it may be considered that irregulated metabolic pathway leading to this situation. Although protein intake was lower for the LEA-LP diet, the percentage of protein metabolism was the highest. However, this situation did not cause a negative protein balance (but the amount of remaining protein was lower when compared to other diets) (see Table 4.3). On the other hand, following of LEA-LP diet increased the percentage of protein oxidation while the percentage of carbohydrate metabolism was higher in the athletes who consumed LEA-LP.

4.3.2. Energy Balance, Energy Availability and Work Performance

The daily energy balance for athletes was calculated by subtracting daily total energy expenditure from daily energy intake. Our results showed that both LEA diets led to a

sustained energy deficit ($p<0.01$ vs. CON; see 4.4), but the energy deficit did not differ between LEA-LP (-6658.4 ± 2109.6 kJ/d [95% Cl: -8609.4-(-)4707.4]) and LEA-HP diets (-5781.0± 623.4 kJ/d [95% Cl: -26591.4-(-)21759.7]); $p= 0.413$]. Energy availability was reduced during LEA-LP (-6658.4 ± 2109.6 kJ/d [95% Cl: -8609.4-(-)4707.4]) and LEA-HP diet (-5781.0± 623.4 kJ/d [95% Cl: -26591.4-(-)21759.7]) when compared to CON (771.5 ± 1915.4 kJ/d [95% Cl: -844.7-2388.2]; $p<0.003$; see Table 4.4).

The daily energy availability was found by calculating the difference between daily energy intake and exercise energy expenditure. Energy availability decreased dramatically when athletes followed LEA-LP (61.5± 9.2 kJ/kg FFM [95% Cl: 52.7-69.9]) and LEA-HP diet (63.6 ± 8.4 kJ/kg FFM [95% Cl: 56.1-71.2]). The energy availability value for athletes was (169.0 ± 10.0 kJ/kg FFM [95% Cl: 159.8-197.5]) during the CON diet (see Table 4.4) and this value was significantly higher than both caloric restriction diet (LEA-HP versus CON: $p= 0.001$, LEA-LP-CON: $p= 0.003$).

Table 4.4. Energy balance and energy availability

	EB (kJ/d)	EA [kJ/kg FFM/day]
CON	771.5 ± 1915.4 [95% Cl: -844.7-2388.2]	169.0 ± 10.0 [95% Cl: 159.8-197.5]
LEA-HP	-5781.0± 623.4 [95% Cl: -26591.4-(-)21759.7]	63.6 ± 8.4 [95% Cl: 56.1-71.2]
LEA-LP	-6658.4 ± 2109.6 [95% Cl: -8609.4-(-)4707.4]	61.5± 9.2 [95% Cl: 52.7-69.9]

Work performance was determined by calculating metabolic heat production and efficiency of metabolism values (see Table 4.5). As shown in Table 4.6, following the caloric restriction diets cause lower work performance when compared to the CON diet. However, there was no statistically significant difference between the work performance for all diets (CON-LEA-HP: $p=0.121$, CON versus LEA-LP: $p=0.093$, LEA-HP versus LEA-LP: $p=0.897$).

Table 4.5. Metabolic heat generation and heat loss due to respiration and perspiration with each type of diet

	Metabolic heat production (kJ/d)	Heat loss (kJ/d)
CON	15157.08 ± 2898.34 [95% Cl: 12476.56-17837.60]	1291630.56 ± 581779.29 [95% Cl: 753574.56-1829686.66]
LEA-LP	12683.70 ± 1378.48 [95% Cl: 11408.72-13958.70]	1223424.35 ± 130349.94 [95% Cl: 1102870.76-1343977.94]
LEA-HP	12837.26 ± 1712.22 [95% Cl: 11253.72-14420.79]	1250858.83 ± 164877.32 [95% Cl: 1098342.74-1403314.92]

Table 4.6. The work performance for each diet

	Work performance (kJ/d)
CON	4911.2 ± 953.8[95% Cl: 4029.00-5793.3]
LEA-LP	4108.4 ± 450.2[95% Cl: 362.0-4524.8]
LEA-HP	4169.4 ± 549.5[95% Cl: 3611.4-4692.4]

Our results indicate that both caloric restriction diets with moderate-intensity exercise led to high-energy deficiency and low-energy availability. According to the literature, 15 kcal/kg FFM/day is risky for an athlete's health since it indicates that energy availability is not adequate to meet the energy demand required to maintain physiological functions [167,219,220]. Energy availability ≥ 40 kcal/FFM/day is sufficient for male athletes [221]. In this study, the CON diet enables an adequate amount of EA for male athletes while the amount of energy deficiency is higher than the recommended amount (400 kcal/d) in the literature in both LEA diets (see Table 4.4) [222]. Low energy availability affects negatively athletes' work performance by causing weakness in muscle strength, fatigue and other physical and physiological disorders [223]. Although our results showed that LEA diets have similar effects on athletes' work performance when compared to the CON diet, the duration of intervention was too short to observe the negative impacts of diet on work performance. Semerciöz *et al.*[185] defined "internal work" as the work performed by internal organs such as the brain, heart, lungs, liver, kidneys, etc. and "external work" as the observable work performance such as running, eating, walking, cycling, etc. Performing both internal and external work requires ATP utilization. Since ATP is utilized to achieve muscle work

performance, heat generation occurs with muscle work performance. The increase in work performance leads to a higher amount of ATP utilization and because of this, a higher amount of heat is generated [46]. The heat generation quantity depends on ambient temperature, food digestion, and muscular activity [224]. In this study, the factor changed was only the amount of calorie intake and protein intake. Therefore, it may be asserted that metabolic heat generation increases depending on calorie intake since the increment in food consumption leads to an increase in basal metabolic rate (BMR) [225]. On the other hand, there was no significant difference among the diets in terms of metabolic heat production.

4.3.3. Entropy Generation and Lifespan Estimation of The Athletes

The entropy generation rate of the athletes was determined by using the macronutrient oxidation rate. The entropy accumulation rate was calculated by subtracting the entropy exportation rate (see Table 4.7) from the entropy generation rate (see Table 4.8). According to statistical analysis, there was no significant difference among diets in terms of entropy generation rate (LEA-LP versus LEA-HP: p=0.322, LEA-LP versus CON: p=0.143, LEA-HP versus CON: p=0.636) and entropy accumulation rate According to statistical analysis, there was no significant difference among diets in terms of entropy accumulation rate (LEA-LP versus CON: p=0.168, LEA-LP versus LEA-HP: p=0.413, LEA-HP versus CON: p=0.576). Each diet has the same effect on the entropy generation rate and accumulation rate.

Table 4.7. Annual entropy exportation rate for each diet

	Entropy exportation rate [kW/kg K]
CON	$2.45 \times 10^{-7} \pm 2.13 \times 10^{-8}$ [2.25×10^{-7}-2.65×10^{-7}]
LEA-LP	$2.33 \times 10^{-7} \pm 1.99 \times 10^{-8}$ [2.05×10^{-7}-2.65×10^{-7}]
LEA-HP	$2.35 \times 10^{-7} \pm 3.28 \times 10^{-8}$ [2.15×10^{-7}-2.52×10^{-7}]

Table 4.8. Entropy generation and accumulation rate for three different diets

	Total Entropy Generation Rate [kW/kg K]	Entropy Accumulation Rate [kW/kgK]
CON	$5.36 \times 10^{-6} \pm 5.21 \times 10^{-7}$ [95%Cl: 4.87×10^{-6}-5.83×10^{-6}]	$5.11 \times 10^{-6} \pm 5.00 \times 10^{-7}$ [95%Cl: 4.65×10^{-6}-5.58×10^{-6}]
LEA-LP	$5.17 \times 10^{-6} \pm 4.74 \times 10^{-7}$ [95%Cl: 4.73×10^{-6}-5.61×10^{-6}]	$4.94 \times 10^{-6} \pm 4.54 \times 10^{-7}$ [95%Cl: 4.52×10^{-6}-5.36×10^{-6}]
LEA-HP	$5.30 \times 10^{-6} \pm 7.01 \times 10^{-7}$ [95%Cl: 4.65×10^{-6}-5.95×10^{-6}]	$5.07 \times 10^{-6} \pm 6.68 \times 10^{-7}$ [95%Cl: 4.45×10^{-6}-5.68×10^{-6}]

The lifespan of the athletes was estimated based on entropy generation and accumulation rate. Lifespan estimations were 72.0 ±7.5 years [95%Cl: 64.7-78.5], 74.0 ± 6.5 years [95% Cl: 67.9-79.8], and 73.0 ± 11.2 [95% Cl: 62.3-83.0] for the CON, LEA_LP, and LEA_HP respectively. The diets influence lifespan estimation equally. Figure 4.5 shows estimated lifespan values for the CON, LEA-LP, and LEA-HP diets.

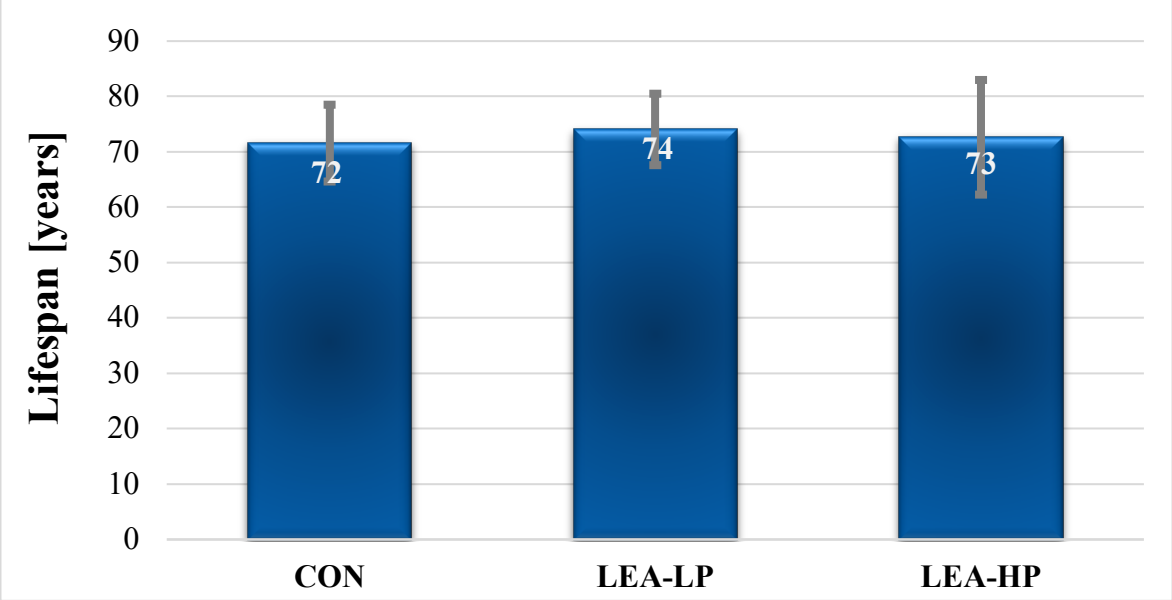

Figure 4.5. Lifespan estimation of the athletes based on diet

(There is no difference among the diets. LEA-HP-CON: p= 0.763, LEA-HP-LEA-LP: p= 0.212, CON-LEA-LP: p= 0.343)

According to Silva and Annamalai [75], the reduction in energy intake resulted in an increase in lifespan. Moreover, fat and carbohydrates do not significantly affect the entropy generation rate while protein has a significant effect on entropy generation. The oxidizing agent acts as an electron acceptor, and the nutrient atoms' electrons are "shuffled" throughout the oxidation reaction. It was recently shown that the ratio between the moles of electrons transferred to oxygen per mole of fuel is 4 times greater than the stoichiometric moles of C-H-O-S fuel. Therefore, for carbohydrates, it's 24 kJ/electron mole; for fat, it's 92 kJ/electron mole. Each electron mole transferred results in the release of 111 kJ/electron mole. Hence, protein is metabolized less efficiently than carbohydrates (nearly η =40%) and fats (η= 10%). Thus, the oxidation of protein leads to higher entropy production [226]. However, in the current study, although energy intake was restricted during the following of LEA_LP and LEA_HP, glycogen and lipids reuse (see Table 4.3) to meet energy requirements caused entropy generation. There was no significant difference in terms of entropy generation because protein oxidation amounts were close to each other even though there is a difference between carbohydrate and fat oxidation for each diet (Table 4.3). An increase in entropy generation and entropy accumulation rates lead to a decrease in lifespan. When the body generates more entropy than exported, the entropy accumulation rate increases in the body. Thus, it leads to ageing and damage in the body. For the first condition, when it was considered the average lifespan of humans in Europe was 79 years by 2019 according to our world in data (https://ourworldindata.org/life-expectancy) [227], all diets decreased average lifespan estimation by increasing entropy generation and accumulation rates. A LEA diet provoked the reuse of glycogen and lipids and their oxidation of them caused more entropy generation. CON diet also led to excess energy intake and thus, increased entropy generation and accumulation rates. Therefore, the lifespan estimation of the athletes decreased for all cases.

For the second (for 5 years of consumption of the LEA diets) and the third conditions for 10 years of consumption of the LEA diets, there is no significant difference among the diets in terms of entropy accumulation for 5 and 10 years of LEA diets, respectively. Lifespan estimation was 89 ± 7[95%Cl: 81-96] years and 89 ± 8[95%Cl: 81-96] years for the CON diet, 89 ± 7[95%Cl: 82-96] years and 89 ± 772.3[95%Cl: 81-96] years for the LEA-LP diet, and 89 ± 8[95%Cl: 82-97] years and 89 ± 8[95%Cl: 81-96]years for the LEA-HP diet, respectively. Table 4.9 presents entropy accumulation until retirement and lifespan

estimation for following the LEA diets for 5 and 10 years. There was no significant difference between the diets in terms of lifespan estimation (CON versus LEA-HP: p= 0.689, CON versus LEA-LP: p= 0.365, LEA-HP versus LEA-LP: p= 0.605 for 5 years of the CR diets consumption and CON versus LEA-LP: p= 0.689, CON versus LEA-LP: p= 0.366, LEA-HP versus LEA-LP: p= 0.605).

Table 4.9. Entropy generation and lifespan estimation for 5 and 10 years of the LEA diet

	Following the LEA diets for 5 years		Following the LEA diets for 10 years	
Diets	Entropy accumulation for 50 years [kJ/kg K]	Lifespan (year)	Entropy accumulation for 50 years [kJ/kg K]	Lifespan (year)
CON	8090.0 ± 719.9 [95%Cl: 7424.3-8755.8]	89 ± 7 [95%Cl: 81-96]	8090 ± 719.9 [95%Cl: 7424.3-8755.8]	89 ± 8 [95%Cl: 81-96]
LEA_LP	8013.5 ± 697.7 [95%Cl: 7368.2-8658.7]	89 ± 7 [95%Cl: 82-96]	8051.7 ± 708.3 [95%Cl: 7305.9-8706.9]	89 ± 772.3 [95%Cl: 81-96]
LEA_HP	8020.2 ± 772.3 [95%Cl: 7305.9-8734.4]	89 ± 8 [95%Cl: 82-97]	8055.1 ± 744.3 [95%Cl: 7366.8-8743.4]	89 ± 8 [95%Cl: 81-96]
Annual entropy generation for the retirement diet	86.6 ± 12.8 [95%Cl: 78.3-95.0]			

Lifespan estimation increased when athletes followed the LEA diets for only 5 and 10 years period, then continued the CON diet until their retirement. Table 4.10 represents the increment in lifespan estimation for the second and third states when compared to the first state. However, our results suggested that lifespan estimation increases when the LEA diets

are consumed only for 5 and 10 years (see Table 4.9 and Table 4.10). Both diet period affects the lifespan estimation similarly.

Table 4.10. The lifespan increment for the second and third situations when compared to the first situation

	Following the LEA diets for 5 years	Following the LEA diets for 10 years
Diets	Increment in Lifespan (year)	Increment in Lifespan (year)
CON	17±5 [95%Cl: 12-22]	17±5 [95%Cl: 12-22]
LEA_LP	16±6 [95%Cl: 11-22]	16±6 [95%Cl: 10-22]
LEA_HP	17±7 [95%Cl: 10-24]	16±8 [95%Cl:8-24]

4.4. LIMITATIONS OF THE STUDY

There were several limitations related to the study. For the first part of the study, we used experimental data obtained from another research. However, we could not access all the necessary data to make calculations. Therefore, we had to assume some values for energy and entropy calculations. Moreover, we could not perform statistical analysis due to a lack of data.

In the second part of the study, we had no experimental data to perform calculations. We researched general athletes' profiles such as age, weight, and height for each sport. Then, the diets were prepared for each athlete group. We made all calculations based on energy and macronutrient intake. For this reason, we had to make some assumptions to perform a thermodynamic analysis.

For the last part of the study, There were several limitations related to the study. We do not have 24 h oxygen consumption, carbon dioxide production amount, and urinary nitrogen level; therefore, we had to make some assumptions to calculate the oxidation rate of macronutrients. There were no data associated with pre-experiment energy and food intake.

Moreover, the duration of experiments was short and we did not have knowledge of the physiological effects of a long-term LEA. In this study, we designed a model to predict its further effect of it on entropy generation and lifespan estimation. Hence, the entropy generation rate pre-experiment was not calculated. Moreover, a larger sample size can enable results that are more accurate. The results of the current study should be evaluated carefully since athletes' muscular development, mental health, and further physiological state were not considered during this study. On the other hand, our results help to understand how energy intake and the type of diet under the influence of exercise would affect the athletes' entropy generation rate and lifespan. This study serves as a guide for further research related to athlete health and performance.

The results of the second and third parts of the study should be evaluated carefully since athletes' muscular development, mental health, and further physiological state were not considered during this study. On the other hand, our results help to understand how energy intake and the type of diet under the influence of exercise would affect the entropy generation rate and lifespan of the athletes. These studies serve as a guide for further research related to athlete health and performance.

Unfortunately, we were not able to show the effects of diets and exercise on an athlete's gut microbiota composition in this study. Therefore, we performed thermodynamic analysis only for an athlete's body and could not assess the gut microbiota subsystem for the superorganism.

5. CONCLUSION

In the first part of the study, the effects of diet-related gut microbiota alterations on human energy and entropy balance were investigated. To perform the study, obese and lean subjects' data for high-caloric and low-caloric diets were used. Energy and entropy balance changes were determined dependent on the percentage of a relative increase and decrease in the Bacteroides and Firmicutes spp. The main findings of the study are presented below.

Gut microbiota serves as a partner with the host to carry out the metabolic activity. Schrödinger and Prigogine's Nobel-winning theories suggest that living systems must import energy and export entropy to maintain their living states. Metabolic heat generation is the major cause of entropy generation in biological systems. The entropic age concept suggests that a fraction of the entropy generated in living beings is accumulated as structural ageing damage in the long term. By carrying out a fraction of the metabolic activity in the gut, its microbiota serves as a vehicle to convey the generated heat and entropy to the faeces, thus reducing the heat generation within the body of the host and its ageing impact. Under the conditions of this study, it would be possible to remove up to 59% of the metabolic entropy with the faeces, without contributing to the ageing of the host. Although entropy removal with the waste from chemical plants is known and discussed very well in the literature, entropy export with faeces with the contribution of gut microbiota, as suggested in the present study, is new to the literature and deserves further attention in future research.

The second part of the study was related to diet-dependent athletes 'lifespan. The special diets were prepared for cyclists, weightlifters, rugby players, and golfers for their active years and then another diet was planned for their retirement period. Employing the diet-based entropic assessment method in the same way as recently reported by Öngel *et al.* (184) suggest that calorie and composition of the diet affect the metabolic entropy generation rates of the athletes depending on their metabolism. It was reported in the literature that the life expectancy of athletes may be affected by the static and dynamic components of the sports they perform. This study may be a starting point for the forthcoming medical studies on athletes' health, longevity and morbidity. The expected average longevity for male athletes was 56 years for a cyclist, 66 years for a weightlifter, 75 years for a rugby player and 92 years for a golfer. If they should start consuming the retirement diet after 50 years of age,

the longevity of the cyclist may increase for 7 years, and those of weightlifters, rugby players and golfers may increase for 22, 30 and 8 years, respectively.

Adequate energy availability is important for athletes to sustain all physiological functions relevant to health and performance. In this study, the relationship between diet types, energy balance, and energy availability was investigated for athletes consuming CON, LEA-LP, and LEA-HP diets. Moreover, the amounts of metabolic heat production, total heat loss, and work performance by utilizing ATP were determined. To perform work, ATP utilization is necessary and ATP is produced by the metabolism of macronutrients. Therefore, work performance and metabolic heat generation rate are associated with each other. Our results showed that work performance was the lowest in the LEA-LP and the highest in the CON. However, these results were not statistically significant. In the study, LEA was induced through the consumption of an LEA diet, while energy deficiency was not observed during CON conditions. Likewise, energy availability was under the normal value required to sustain physiological functions for both LEA diets. Although our results show that the effects of LEA and CON on work performance and lifespan of the athletes were similar, long-term LEA may cause a decrease in work performance as well as low lifespan estimation due to high entropy generation. As mentioned above, low energy availability causes health problems such as muscle loss, the reduction in bone density, fatigue, injury, and weakness of some physiological functions. Extreme calorie restriction diet-induced oxidation of glycogen and stored lipids to supply sufficient energy to work. As a result, low energy availability and high energy intake increased entropy generation and decreased lifespan. A balanced diet that prevents a state of LEA can also have positive effects on long-term outcomes, which are typically not considered in sports nutrition, such as longevity.

6. FUTURE PROSPECTS

Physiological processes such as muscle contraction, nervous, gastrointestinal and reproductive functions, absorption of ions and detoxification of exogenous substances require the consumption of ATP, most of these processes are accompanied by the dissipation of heat and the dissipated heat cause the generation of entropy in the system. Early diagnosis and treatment of various diseases (cancer diseases, metabolic diseases and ageing diseases such as Alzheimer's) that be observed in the future are possible by quantifying entropy generation related to the stress on individual organs in living systems.

This study will contribute to the preparation of healthy diets for different athlete groups by taking into account their energy balance and entropy balance changes. Moreover, by considering the effects of gut microbiota alterations on the human homeostatic mechanism, especially on energy homeostasis and lifespan, exercise and diet plans can be prepared to manipulate gut microbiota composition positively.

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