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Review Article

Influence of Exercise or Physical Activity in the Angiogenesis Process: Integrative Review

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Abstract

In order to understand the relationships of the influence of physical activity in the angiogenesis process, this review aims to recruit in the last ten years the evidence on this topic. The study data collection took place between February 20 and March 20, 2020. The electronic databases used to search the articles was PubMed (National Library of Medicine and National Institutes of Health). We used the keywords: angiogenesis, angiogenic effect, vascular endothelial growth factor (VEGF), physical activity, physical exercise, exercise and training, in the English languages, accompanied by the expression AND and selected through DeCS (Descriptors in Health Sciences). The performance of physical activity, (Figure 2), whether aerobic or resisted with load, promotes in the body an increase in pro-angiogenic factors such as: IL-6, Ang 1 and 2, VEGF, PDGF, FGF and stimulation of their receptors, being, respectively: IL -6Ra, TIE-2, VEGFR-1 and 2, PDGFR, FGFR. Higher levels of Adropine also encourage the expression of VEGFR-2. The activation of IL-6Ra, VEGFR-1 and 2 receptors elevates, together with increased expression of miR-126, a small fragment of non-coded RNA, the enzyme PI3k (Phosphoinositide 3-kinase). This increased enzyme induces the expression of protein Kinase B (Akt) which plays a fundamental role in cell metabolism via the mTOR pathway. We will then have the formation of MMP-2, MMP-9, VEGF, CD31 and HIF-1α, the latter being directly stimulated by the increase in NO. In this way, those responsible for proliferation, migration, survival and cell permeability will be present, necessary for improvements in the levels of angiogenesis to occur. It was possible to conclude that the physical activity induced in both experimental and human models favored the process of angiogenesis in organisms by increasing pro factors and decreasing anti-angiogenic factors, regardless of pre-existing comorbidities and previous sedentary lifestyle.

Keywords: Physical activity; Exercise; Angiogenesis; Vascular Endothelial Growth Factor

Introduction

The word “angiogenesis” was derived from the Greek where “angio” means blood vessel and “genesis” means production or birth, together they refer to the generation of blood vessel within the body. Historically, the term angiogenesis was first used to describe the growth of endothelial shoots from pre-existing post-capillary veins. Over time, this term has been used to denote the process of growth and remodeling of the primitive network of a vascular complex [1]. The vascular system is responsible for the supply of nutrients and oxygen in an organism. New blood vessel formation or neovascularization is divided into two components like vasculogenesis and angiogenesis. The vasculogenesis process is the formation of blood vessels from hemangioblasts that differentiate into mature blood and endothelial cells [2]. Angiogenesis is the process of forming new blood vessels from a pre-existing vascular network, by capillary sprouting [3]. Vasculogenesis ascends the heart and the first primitive vascular plexus within the embryo and in the surrounding membranes, considering that angiogenesis is responsible for the remodeling and expansion of this network.

During this process, mature endothelial cells are divided and incorporated into new capillaries. The signaling of vascular endothelial growth factors (VEGF) is necessary for the complete performance of vasculogenesis and angiogenesis [2,4].

The health benefits of regular physical activity are present in several chronic diseases, including cardiovascular disease, diabetes, hypertension and cancer [5-8]. However, physical inactivity is a risk factor for several pathological conditions, including obesity, hypertension, atherosclerosis and cancer [9-11]. Physical training is known to profoundly alter the morphology of blood vessels along the arterial tree [12-14]. Exercise provides increases related to the quantity (angiogenesis) and the diameter (arteriogenesis) of the arterial blood vessels in the skeletal muscle and in the myocardium. These changes in the architecture of the vascular tree are probably associated with functional changes and improved blood flow to the organ [15-18]. Changes in vascular morphology induced by physical exercise in healthy individuals [15,16] are extremely dependent on the size of the initial vessel. A greater number of vessels in response to training, angiogenesis, appears to occur on the level of very small capillaries and arterioles (<40 μm in diameter), but not in large arteries. The increase in capillary density occurs just after the beginning of the exercise and is transient. A similar pattern was observed in very small arterioles (<20 μm in diameter) and slightly in larger arterioles (20-40 μm in diameter) an increase in the number was also observed [19].

The molecular mechanisms underlying exercise-induced angiogenesis are not fully understood. It has been suggested that growth factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF) and angiopoietins (ANG) as well as their corresponding receptors are involved. In addition, the proteases necessary for the degradation of the capillary basement membrane such as matrix metalloproteinases (MMPs), urokinase, tissue plasminogen activator probably contribute to the mechanism of the emergence of angiogenesis [16,20,21]. Interestingly, some of these proteases appear to allow and/or facilitate the mobilization of endothelial progenitor cells (EPCs) from the bone marrow. It has become apparent that exercise can increase the number of circulating EPCs in animals and humans, and these cells are known to have a large capacity for neovascularization, a process that appears to be critically dependent on the protease cathepsin L [22,23]. In order to understand the relationships of the influence of physical activity in the angiogenesis process, this review aims to recruit in the last ten years the evidence on this topic.

Methodology

In the present study, an integrative review was conducted, which consists of research that allows the evaluation, synthesis and knowledge about a phenomenon from evidence, aiming to produce an overview of complex concepts, theories or relevant health problems from studies pre-existing, enabling the intervention proposal [24,25]. For the selection of articles, 6 methodological steps were carried out, namely: 1. elaboration of the guiding question or research hypothesis, that is, the problem was identified, the search engine and the keywords or keywords were presented; 2. establishment of the inclusion and exclusion criteria of the articles to be selected to compose the sample; 3. exploratory reading of the titles and abstracts of the articles for pre-selection; 4. analytical reading of the articles in order to compile, analyze and categorize the information; 5. interpretation of results. 6. synthesis followed by the presentation of the identified results, which permeate the guiding question [26].

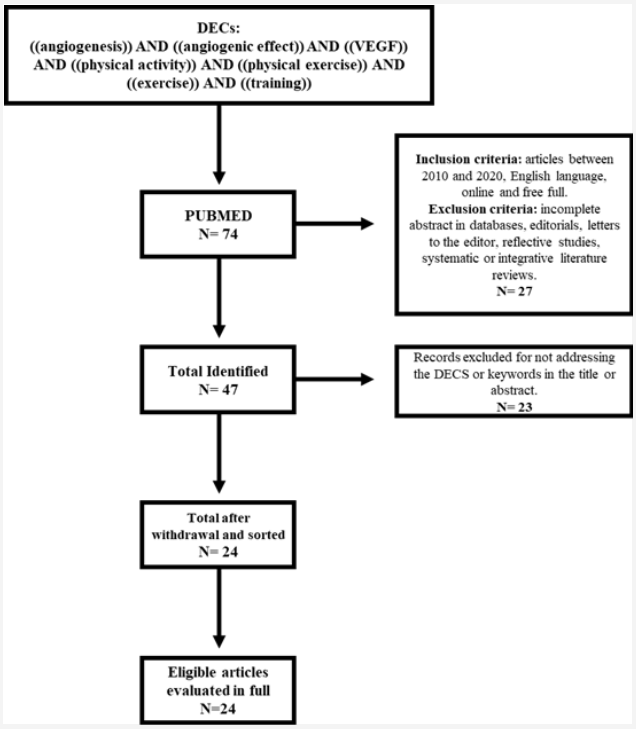

Figure 1: Publication Selection Flowchart.

Therefore, in this study it was decided to search for the concepts: angiogenesis, angiogenic effect, vascular endothelial growth factor (VEGF), physical activity, physical exercise, exercise and training. From these concepts, the guiding question was defined: what is the scientific evidence available in the literature on the relationship between physical activity and events related to the angiogenesis process. After formulating the question to be researched, a bibliographic survey was carried out on the PubMed platform. The survey of the study took place between February 20 and March 20, 2020. And the selection of texts proceeded with searches on the platform, using the filters available for texts published between 2010 and 2020. For the selection of publications, the following were adopted inclusion criteria: scientific articles, published in the English language, between 2010 and 2020, available online and free of charge in full. Articles with no abstract in the database or incomplete, editorials, letters to the editor, reflective studies, systematic or integrative literature reviews were excluded. After defining the guiding question, location and selection of articles, 74 publications potentially eligible to be included in this review were identified. After applying the inclusion and exclusion criteria, the sample consisted of 47 publications, the abstracts of 24 records were analyzed to see if they would meet the eligibility criteria and answer the question that guides this review, thus excluding 23 records and only 24 were analyzed in full to confirm eligibility for quantitative synthesis and data analysis according to the selection flowchart (Figure 1).

Result and Discussion

The proposed review aimed to associate the practice of physical activity and angiogenic parameters, such as VEGF synthesis, expression of its receptors (VEGFR), as well as the expression of angiogenesis inducing molecules and involved in the quantification of microvascular density (CD31), as well as the synthesis of chemical mediators involved in this process. Thus, we divided the reviewed studies into two groups, namely: studies with experimental models and studies involving human beings.

Table 1 lists the studies with experimental models of physical activity and angiogenic study. Thus, Lee and Cols (2018) [27], report that the performance of voluntary wheel exercises performed by mice for 6 weeks resulted in an increase in angiogenic factors. As well as, moderate intensity exercises performed by mice, during 8 weeks, increased the gene expression of angiogenic factors and decreased insulin resistance [28]. In addition, in the performance of physical activity performed by elderly mice, for 10 weeks, an increase in VEGF, an increase in BFR was observed, occurring a cardiac physiological remodeling corresponding to the demand [29]. The treadmill practice performed by mice is correlated to the increased expression of angiogenic factors, both in healthy animals and in animals with previous comorbidities [30]. Likewise, there was an improvement in the levels of cardiac markers correlated with physical activity performed on a treadmill by male mice at moderate intensity, for 8 weeks [31]. The practice of aerobic exercises performed by male mice, for 15 minutes/day for 8 weeks, is directly related to an improvement in cardiac angiogenesis and in the intramuscular capillary density [32]. Still, the practice of AET performed by male mice, which consists of swimming sessions of 60 minutes, 5 times a week, for 10 weeks, proved to be effective in vascular remodeling, being an important therapeutic target for the treatment of several cardiovascular diseases [33]. Individuals who performed physical exercise in swimming mode, at different intensities, obtained an increase in angiogenic factors, some of them (VGEF-B, MEF-2, MMP-2) with greater proportional increases in intensity and, on the other hand, ANGPT-1 and HDAC4 showed more satisfactory results at moderate exercise intensity [34].

Table 1: List of articles that investigated the influence of physical activity on the angiogenesis process in experimental models.

Reference	Type of Disease	Intervention – Physical Activity	Studied Variables	Main Results (Trained vs Sedentary)	Conclusions
Lee [27]	Not applicable	Male mice C57BL/6J Voluntary wheel during 6 weeks	VEGF	↑ VEGF	The angiogenic gene expression is altered by physical training, for the VEGFA, Ang1 and Ang2 genes, being correlated to the adipose tissue deposit.
			Ang1	↑ Ang1	
			Ang2	↑ Ang2	
			PDGF-B	↑ PDGF-8	
			BAT	↔ BAT	
Shin, et al. [28]	Not applicable	32 mice Sprague-Dawley, obesity-induced. Performed moderate intensity exercises for 8 weeks.	PGC-1α,	↑PGC-1α,	Regular exercise seems to act positively on glycemic control and insulin sensitivity through the signaling pathway of angiogenesis, both in mice under normal conditions and also in obese mice.
			IL-6	↑IL-6	
			IL-15,	↑ IL-15,	
			mTOR,	↑mTOR,	
			VEGF	↑VEGF	
			FLT1	↑ FLT1	

Naderi-boldajia, et al. [29]	Cardiac Function	Elderly mice. Low intensity treadmill for 10 weeks	VEGF,	↑VEGF,	The findings suggest that BFR plus exercise by improving angiogenesis, physiological cardiac remodeling and matching oxygen demand / supply may promote cardiac performance in elderly rats.
			Flt-1	↑ Flt-1	
			Kdr	↑ Kdr	
			BFR	↑ BFR	
Hassan and Kamal [36]	Not applicable	40 Male Mice 1st Week: Swimming 30min/ day 2nd-6th week: Diving with external weight 4 series of 10 dives	VEGF	↑VEGF	Physical exercise increases the VEGF angiogenic marker, thus being related to the improvement of cardiac performance, hemodynamics, and angiogenesis.
Erekata, et al. [30]	Not applicable	Treadmill 18m/min 40min/day 5 days/week	VEGF	↑VEGF	Physical exercise is related to the increase in the angiogenesis process both in healthy individuals and with individuals with comorbidities such as DM1.
Jesus, et al. [32]	Not applicable	40 Wistar Male Mice Aerobics 15 min/day 8 weeks	VEGF	↑VEGF	Physical exercise is related to the increase in the angiogenesis process both in healthy individuals and with individuals with comorbidities such as DM1.
			Capillary Density	↑Capillary Density	
Broderick, et al. [31]	Not applicable	Male Mice Treadmill Moderate intensity 5 days 8 weeks	PCR	↑ PCR	Physical exercise improves the levels of cardiac markers of angiogenesis, insulin resistance and endothelial dysfunction, regardless of obesity, hyperglycemia and systemic inflammatory reactions.
			IL-6	↑ IL-6	
			NO	↑ NO	
			VEGF-A	↑ VEGF-A	
			HIF-α	↑ HIF-1α	
Ranjbar, et al. [39]	Cardiac	Male Mice Treadmill at 17m/min 10 to 50 min/day 10 weeks	VEGF	↑ VEGF	Angiogenic factors increased and angiostatic factors decreased. The density of capillaries and arterioles increased. Supplementation with L-Arginine, generated an increase in the number of intra-fiber capillaries.
			Angiostatin	↓ Angiostatin	
			Caspase-3	↓ Caspase 3	
Bellafiore, et al. [40]	Not applicable	63 Swiss Rats Exercise Time: 15, 30 and 45 days with Gradual increase in intensity	VEGF	↑ VEGFR-1	VEGFR-2, Flk-1 increased progressively in the groups that performed exercises. VEGFR-1, Flt-1 and HIF-1a increased in the T15 group. NO3 increased in groups that practiced exercises after 15/30 days.
			VEGFR-1	↑ VEGFR-2	
			VEGFR-2	↑ Flt-1	
			Flt-1	↑ Flk-1	
			Flk-1	↑ HIF-1α	
			HIF-1a	↑ NO	
			NO		
Soori, et al. [35]	Cardiac	24 Male Mice 6 weeks HIIT (high intensity interval training) e CET (Continuous exercise training)	FGF-2	↑ FGF-2	Both types of training decreased myocardial fibrosis related to the aging process of rats and increased molecules linked to angiogenesis in the heart and endothelial tissue. HIIT induced a greater increase in VEGF.
			VEGF	↑ VEGF	
			Adropin	↑ Adropin	
			Myocardial fibrosis	↓ Myocardial fibrosis	
Gomes, et al. [41]	Not applicable	21 rats: 5 lean sedentary; 5 lean and physically active; 5 sedentary obese and 6 active obese Swimming 1hr / day, 5x / week for 10 weeks:	PI3KR2, PI3K,	↑miR-126	PI3K, VEGF, and eNOS; miR-126 found low in sedentary obese, increase in lean active and regularized values in active obese. PI3KR2, increased in obese compared to lean and had values re-established in active obese.
			VEGF, eNOS; miR-126	↑ VEGF	
				↓ PI3KR2	
				↑PI3K	
				↑eNOS	

Ardakanizade [34]	Not applicable	18 male rats 1 to 4.5 hours of swimming /day 5x /week for 5 to 10 weeks	HPRT-1; VEGF-B; ANGPT-1; MMP-2; HDAC4; MEF2C	↑VGEF-B, ↑ MEF-2, ↑MMP-2, ↑ANGPT-1 ↑HDAC4	↑ VGEF-B, ↑ MEF-2, ↑ MMP-2, progressive increase according to the intensity of the exercise, ↑ ANGPT-1 ↑ HDAC4 were higher in individuals submitted to medium intensity followed by individuals submitted to high intensity.
Roudier, et al. [37]	Not applicable	16 female rats, 9 female rats of middle age and 22 obese diabetic rats: treadmill 25m / min inclination of 4%, 1hr / day, 5x / week for 8 weeks	Mdm2, CD31, VEGF-A	↑Mdm2 ↑ CD31 ↑Vgef-A	↑ Mdm2 ↑ CD31 and ↑ Vgef-A were increased in physically active individuals, indicating an increase in angiogenic levels
Tian, et al. [38]	Cardiac injury	140 adult male rats. Divided into 4 groups. 1 group performed a monitored treadmill for 8 weeks. 2 first -30 min / day at 11 m / min The subsequent training was carried out at a moderate level in each training period (5 days per week). The others remained sedentary during the study.	HSF1 and VEGF/ HIF-1 alfa anti-CD31	↑HSF1 ↑ CD31 ↑VEGF	Study clarifies the process by which physical training improves cardiac remodeling initiated by CAT and systolic disease and a crucial role in the lasting preservation of HSF1-dependent heart disease micro-ontogeny in response to physical training.
Fernandes, et al. [33]	Cardiac injury	21 rats separated into 4 groups. All submitted to the AET protocol. This consisted of swimming sessions of 60 mi in duration, 5 days a week, for 10 weeks, with a caudal workload of 4% of body weight.	VEGF, VEGFR2 e CD31	↑VEGFR2 ↑ CD31 ↑VEGF	Understanding the contribution of these miRNAs to the entire spectrum of vascular disease remodeling processes is important, especially since these miRNAs can have great potential therapeutic targets for the treatment of various cardiovascular diseases.
Olfert, et at. [42]	Cardiac injury	16 rats, divided into 2 groups of 8. One group performed the exercise training consisting of a treadmill for 1 h / day, 5 days / week, totaling 6 weeks. The other group remained sedentary.	VEGF and PFK	↑PFK ↑VEGF	These data demonstrate a vital role for myocyte VEGF at the start of the complex series of events necessary for exercise-induced skeletal muscle angiogenesis and provide additional evidence that skeletal muscle capillarity is one of the main factors contributing to overall exercise performance.

Finally, rats with heart disease undergoing physical training, high intensity interval (HIIT) and continuous rhythm (CET), presented a decrease in myocardial fibrosis related to the aging process, in addition to increasing the amount of molecules linked to angiogenesis in the heart and in the endothelial tissue. Being that HIIT training induced a greater increase in VEGF [35]. In this sense, aerobic and resistance exercise with load also promoted, in the study by Hassan and Kamal (2013) [36], improvement in cardiac performance, hemodynamics and angiogenesis, related to the VEGF marker. The practice of physical exercise on a 4% inclined treadmill, for 1 hour, 5 times a week, for 8 weeks, in female mice, being diabetic and obese, proved to be effective in increasing angiogenic levels [37]. With the practice of physical activity performed on a treadmill by male rats with varying intensity (from mild to moderate), an improvement in cardiac remodeling initiated by CAT is observed [38]. In addition, it was found that performing a 17m / min intensity mat in male rats, from 10 to 50 minutes / day, for 10 weeks, decreased angio-static factors and increased angiogenic factors [39]. In addition, the practice of exercise performed by mice with a gradual increase in intensity progressively increased the angiogenic factors VEGFR-2 (FLK-1) [40].

Likewise, obese and normal weight individuals, whether sedentary or not, were submitted to physical activity in the swimming modality. The results obtained by Gomes et al. (2017) [41], indicated an increase in pro-angiogenic factors in physically active individuals, this increase being higher in individuals with normal weight when compared to obese individuals. Analyzing the practice of physical exercises on a treadmill, performed by male rats to the detriment of sedentary mice, it can be concluded that those who exercised, obtained a significant increase in angiogenic factors when compared to those who did not practice [42].

Table 2 summarizes the studies involving human beings, in which the practice of physical activity with the use of an exercise bike, caused an increase in cytokines and angiogenesis and biogenesis factors in skeletal muscle cells [43]. Aerobic physical

activity performed for 12 weeks promoted an increase in muscle capillarity, an increase in VEGF and VEGFR, an increase in HIF-α and α-tubulin. However, protein supplementation was not effective in changing these parameters, but the practice of physical activity [44].

Table 2: List of articles that investigated the influence of physical activity on the angiogenesis process in human trials.

Reference	Type of Disease	Intervention - Physical Activity	Studied Variables	Main Results	Conclusions
Larkin, et al. [48]	Muscle microlesions	6 young adults 120 unilateral knee extensions with 40% of maximum load	VEGF	↑VEGF	Acute BFR increases post-exercise mRNA expression related to skeletal muscle angiogenesis, plausibly in response to changes in muscle Hb concentrations.
			VEGF-R2	↑VEGF-R2	
			NO	↑ NO	
			BFR	↑ BFR	
Taylor, et al. [43]	Not applicable	Exercise Bike High Intensity Until muscle fatigue is reached (8-10min)	PGC-1α, VEGF, HIF1α	↑PGC-1α	After the practice of high intensity exercise, there was an increase in cytokines and angiogenesis and biogenesis factors in skeletal muscle cells
				↑VEGF	
				↑HIF1α	
Holloway, et al. [49]	Not applicable	20 Young men Weight Resistance Workout 10 Individuals 20-25 repetitions per set (low load) 10 Individuals 8-12 repetitions per set (high load)	VEGF, eNOS	↑VEGF	After verification of biopsies and serum tests, it is concluded that both in individuals submitted to high repetition or high load exercises, there is an increase in muscle mass and angiogenesis factors
				↑eNOS	
Izzicupo, et al. [46]	Not applicable	Walking 13 weeks	VEGF	↓ IL-8	Walking training reduces the inflammatory state and leads to a significant improvement in serum angiogenic properties.
			IL-8	↓ TNF-α	
			TNF-α	↓ Leptin	
			DHEA-S	↓ Resistin	
			Leptin	↑ DHEA-S	
			Resistin	↑ Adiponectin	
			Adiponectin		
Van Pelt, et al. [45]	Not applicable	Regular physical exercise: Treadmill Exercise Bike	VEGFA	↑ VEGFA	Exercise initiates increases in factors related to angiogenic processes and can promote changes in inflammation of macrophages in subcutaneous adipose tissue.
			CD14	↑ CD14	
			CD31	↑ CD31	
			IL-6	↑ IL6	
Holloway, et al. [44]	Not applicable	Young men aerobic physical activity for 12 weeks, with protein supplementation	Muscle	↑musclecapillarity, ↑eNOS,	There was no difference in these markers in the group supplemented with proteins and the placebo, however there was an increase in vascularization and gene expression in both groups.
			capillarity, eNOS, VEGF, VEGF receptor, HIF1-a a-tubulin	↑VEGF	
				↑VEGF receptor ↑HIF1-a	
				↑a-tubulin	
Hoier, et al. [47]	Muscle injury	Serial biopsies in young adults, men, always at rest, during the 60-minute cycling exercise and in the recovery phase.	VEGF, sVEGFR-1 , MMP9, Ang2, Ang2 / Ang1, mRNA of Tie2 TSP-1	↑ MMP9	Acute exercise leads to an increase in the gene expression of pro and antiangiogenic factors, and we propose that a transient positive regulation of antiangiogenic factors serves to modulate the angiogenic process to prevent excessive hair growth. In addition, leading to increased capillarization, baseline levels of protein and mRNA, as well as the acute increase induced by exercise in mRNA for various angiogenic factors, remained virtually unchanged, suggesting a similar level of angiogenic potential in untrained and trained muscles.
				↑ Ang2,	
				↑Ang2 / Ang1	
				↑VEGF	
				↑ mRNA of Tie2	
				↑ TSP-1	

Beijer, et al. [50]	Muscle injury	Physical exercise: consisted of squats weighing 10 kg and increased heel weight of 15 kg	MMP-2, MMP-9, VEGF and endostatin	↑MMP-2, ↑MMP-9, ↑VEGF ↑endostatin	In summary, data show that exercise leads to transient increases in circulating pro-angiogenic markers and, in addition, the proliferation of endothelial cells in vitro is increased by serum factors obtained acutely after exercise. However, superposition of vibrations to resistance exercise decreases the concentrations of VEGF in circulation after exercise, which supposedly results in reduced endothelial cell proliferation in vitro, that is, the superposition of a vibration stimulus to resistance exercise may not be beneficial for the triggering of angiogenic inducing signaling pathways in skeletal muscle.

Positive results regarding the induction of angiogenesis mediators were reported in the study by Van Pelt, et al. (2017) [45], in which regular physical exercises, including: physical maintenance on a treadmill and exercise bike, promoted changes in inflammation of macrophages in the subcutaneous tissue and increased levels of VEGFA, CD31, CD14 and IL-6. Walking as the physical activity of choice for 13 weeks reduces the inflammatory state and significantly improves serum angiogenic properties. A reduction in IL-8, TNF-α, Leptin, Resistin, Adiponectin and an increase in DHEA-S were evidenced [46].

On the other hand, when performing serial biopsies in young adults at rest, after cycling for 60 minutes, Hoier and Cols (2012) [47], evidenced despite the slight increase in TIE-2, TSP-1, Ang2, MMP-9 and VEGF, which would practically not influence the angiogenic potential of trained muscles. Regarding the practice of resistance exercises, Larkin and Cols (2012) [48], show that the acute restriction of blood flow in patients with muscle microlesions, who performed knee extensions with load showed an increase in mRNA related to skeletal muscle angiogenesis in response to changes in hemoglobin concentration in skeletal muscle. In addition, resisted physical activity with weight, either with high load and little repetition, or with little load and high repetition, promoted an increase in muscle mass and also in angiogenic factors [49]. In individuals undergoing resistance physical exercise, there is a transient increase in pro-angiogenic markers and an increase in cell proliferation in vitro. However, the overlapping of vibrations to that same exercise results in decreased proliferation of cells by decreasing the circulating VEGF, and may therefore not be beneficial for triggering angiogenesis-inducing signaling pathways [50].

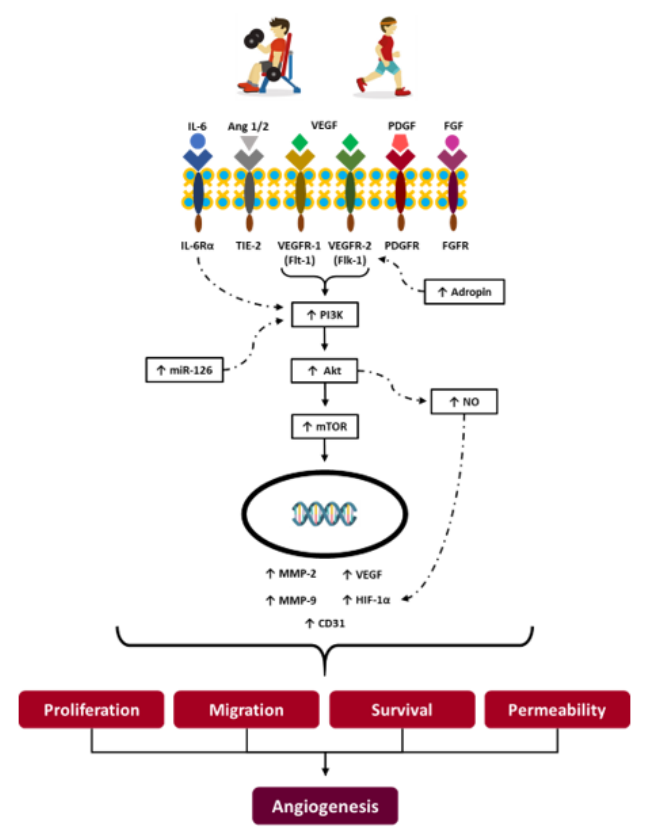

Figure 2: Representation of the influence of physical activity on signaling pathways recorded in the angiogenesis process.

The performance of physical activity, (Figure 2), whether aerobic or resisted with load, promotes in the body an increase in pro-angiogenic factors such as: IL-6, Ang 1 and 2, VEGF, PDGF, FGF and stimulation of their receptors, being, respectively: IL -6Ra, TIE-2, VEGFR-1 and 2, PDGFR, FGFR. Higher levels of Adropine also encourage the expression of VEGFR-2. The activation of IL-6Ra, VEGFR-1 and 2 receptors elevates, together with increased expression of miR-126, a small fragment of non-coded RNA, the enzyme PI3k (Phosphoinositide 3-kinase). This increased enzyme induces the expression of protein Kinase B (Akt) which plays a fundamental role in cell metabolism via the mTOR pathway. We will then have the formation of MMP-2, MMP-9, VEGF, CD31 and HIF-1α, the latter being directly stimulated by the increase in NO. In this way, those responsible for proliferation, migration, survival and cell permeability will be present, necessary for improvements in the levels of angiogenesis to occur.

Conclusion

Physical activity was of fundamental importance in inducing angiogenesis. Through these studies, it was possible to notice that both in experimental models and in human beings, foods or comorbidities, the practice of physical exercises, either resistant to loads or aerobics, considerably improved the levels of vascular evaluation, clinical factors, expression enzyme and its receptors. In addition, anti-angiogenic factors apply at the highest levels in those who remain sedentary, corroborating the idea that the practice of physical activity is of paramount importance for neovascular formation, or that it may possibly cause a determining factor in the quality of life and health of individuals.

Acknowledgement

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Conflict of Interest

No conflict of interest.

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