J Phys Fitness Sports Med, **1(1)**: 5-16 (2012)

**JPFSM:** ***Review Article***

# Effect of exercise on HIF-1 and VEGF signaling

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Received: February 2, 2012 / Accepted: February 14, 2012

***Abstract*** This review summarizes the literature describing the significance of various conditions, such as hypoxia, oxidative stress, and, above all, physical exercise, in the hypoxia-inducible factor-1 (HIF-1) and vascular endothelial growth factor (VEGF) signaling pathway mainly in skeletal muscle. HIF-1α acts as a master regulator for the expression of genes involved in the hypoxia response of most mammalian cells. Namely, HIF-1α initiates transcription of various hypoxia-adaptive genes, such as angiogenesis, glycolysis, and erythropoiesis, after the formation of heterodimer with HIF-1β. Among them, VEGF is the most potent endothelial specific mitogen, which recruits endothelial cells into hypoxic foci and avascular area and stimulates their proliferation. The study on acute exercise shows that several components of the HIF-1 pathway, involving VEGF and erythropoietin, are activated in response to acute changes in oxygen demand in human skeletal muscle, suggesting that oxygen sensitive pathways could be relevant for adaptaion to physical activity by increasing capillary growth. Also, the effects of endurance training on the activity of the HIF pathway in human skeletal muscle under hypoxic conditions appear to be definitely higher than those under normoxic conditions, indicating that combining hypoxia with exercise training appears to improve some aspects of muscle $O_2$ transport and/or metabolism. On the other hand, increased levels of reactive oxygen species (ROS) due to physical exercise induce the expression of peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α), which regulates mitochondrial biogenesis in multiple cell types, resulting in increases in VEGF expression and subsequent angiogenesis, strongly suggesting HIF-1α-independent regulation of VEGF and angiogenesis. Thus, the precise relationship among exercise, the HIF-1 pathway including VEGF, PGC-1α, and ROS needs further study.

***Keywords*** : exercise, hypoxia, HIF-1, VEGF, PGC-1α, reactive oxygen species

## Introduction

Hypoxia-inducible factor-1 (HIF-1) was discovered in 1992 as the transcription factor of the human *EPO* gene encoding erythropoietin (EPO)[1]. HIF-1 is a heterodimeric protein composed of an oxygen-regulated subunit HIF-1α and a constitutively expressed subunit HIF-1β. HIF-1α is hydroxylated by prolyl hydroxylase 1-3 (PHD1-3) on proline residues (Pro402 and Pro564) immediately after *de novo* synthesis[2]. This modification facilitates the binding of von Hippel-Lindau (VHL) E3 ubiquitin ligase complex with HIF-1α, and resultant ubiquitilation and degradation by 26S proteasome. However, when the intracellular oxygen level is reduced, the enzymatic activities of PHDs are inhibited; and this leads to protein stabilization and nuclear translocation of HIF-1α, wherein HIF-1α initiates transcription of various hypoxia-adaptive genes involved in angiogenesis, glycolysis, erythropoiesis, and catecholamine biosysnthesis, after the formation of the active heterodimer with HIF-1β[3] (Fig. 1)[4]. In contrast, there is growing evidence that HIF-1α protein stability is regulated by oxygen-independent mechanisms[5]. For example, acute exercise is accompanied by regional and systemic reduced partial pressure of oxygen as well as acidosis, oxidative stress and heat, all of which are stimulatory factors of HIF-1α[6].

To date, more than 100 genes are identified as the transcriptional target of HIF-1[7]. In addition, more than 2% of all human genes are directly or indirectly regulated by HIF-1 in arterial endothelial cells[8]. Among them, vascular endothelial growth factor (VEGF) is the most potent endothelial specific mitogen, which recruits endothelial cells into hypoxic foci and avascular area and stimulates their proliferation[9]. Actually, homozygous deletion of the *Hif1a* gene encoding HIF-1α in mice results in the arrest of embryonic development at day 8.5 and embryonic

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lethality by day 10.5 with major cardiac malformations, vascular regression, and reduced erythropoiesis[10-12]. Furthermore, homozygous deletion of the *Arnt* gene encoding HIF-1β also results in embryonic lethality at midgestation with defective vascularization[13]. Thus, HIF and VEGF signaling is essential for the maintenance of the vascular density and oxygen supply in tissue hypoxia.

This review focuses on the significance of various conditions, such as hypoxia, oxidative stress, and, above all, physical exercise, in the HIF-1α and VEGF signaling pathway mainly in skeletal muscle.

## Hypoxia in skeletal muscle

A gradient of oxygen partial pressure ($pO_2$) exists within the body, due to approximately 160 mmHg in inspired gas, approximately 115 mmHg in arterial blood, and approximately 38 mmHg in capillary blood[14]. Within tissues, the $pO_2$ gradient depends on the distance of cells from closest $O_2$-supplying blood vessel and the metabolic activity and consequent $O_2$ consumption of the resident cells[15]. For instance, intramyocellular $pO_2$ falls to as low as 3.1 mmHg under normoxia and 2.1 mmHg under hypoxia, respectively[14]. Mitochondria house the final biochemical steps in the production of reducing equivalents that react at the terminal oxidases of the respiratory chain with molecular oxygen provided by the respiratory system from the environment. In mitochondria, $O_2$ finally disappears and oxygen partial pressure ($pO_2$) goes to zero (Fig. 2)[4]. Mitochondria thus are an effective oxygen sink and this allows organisms to use all of the available oxygen partial pressure ($pO_2$) of the actual environment to drive the respiratory cascade from lungs through circulation to the mitochondria[16].

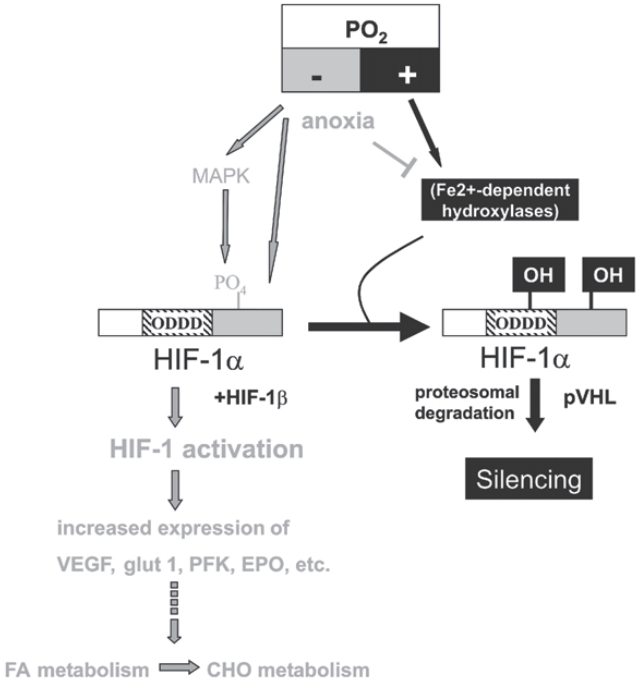


**Fig. 1** HIF-1α-mediated oxygen sensor and hypoxia-inducible gene expression[4]. Oxygen stabilizes hypoxia-inducible factor 1α (HIF-1α) through $Fe^{2+}$-dependent proline hydroxylases and asparaginyl hydroxylase(s) which hydroxylate HIF-1α within its oxygen-dependent degradation domain (ODDD) and C-terminal portion, respectively. Such modification causes recruitment of the von Hippel-Lindau tumour-suppressor protein (pVHL), which targets HIF-1α for proteosomal degradation thereby silencing HIF-1α activity. Conversely, hypoxia causes a stabilization of HIF-1α and activates the MAPK pathway which enhances the transcriptional activity of HIF-1α through phosphorylation. Both mechanisms contribute to transcriptional activation of downstream angiogenic factor (VEGF), erythropoietin (EPO), glucose transporters (glut 1 and 3) and glycolytic genes (PFK) via HIF-1α/HIF-1β dimers (HIF-1). Moreover, lack of oxygen (anoxia) causes HIF-1α stabilization, possibly by reducing the activity of hydroxylases by depleting their substrate $O_2$.

HIF-1α acts as a master regulator for the expression of genes involved in the hypoxia response of most mammalian cells[1,17]. Nevertheless, it is clearly expressed in various tissues such as the brain, kidney, liver, heart, and skeletal muscle in mice kept in a normoxic condition (21% $O_2$), whereas it is undetectable in the lungs[18]. Further, when mice were kept in extreme hypoxia (6% $O_2$), the expression levels of HIF-1α in the brain, kidney, liver, heart, and skeletal muscle were significantly higher, while expression in the lungs was not affected[18,19]. These findings indicate that there is a clear $pO_2$ gradient between the lungs and other tissues, and that with the exception of relatively well-oxygenated lungs, low $pO_2$ and HIF-1α play physiologically essential roles in homeostasis of various tissues.

Moreover, Mounier et al.[20] have shown, in untrained human skeletal muscle under normoxic conditions, higher HIF-1α protein expression in predominantly oxidative muscles than in predominantly glycolytic muscles. The HIF-1α mRNA expression pattern, however, was not in agreement with the HIF-1α protein level. Interestingly, none of the HIF-1α target genes, like the most studied angiogenic factor involved in muscle angiogenesis, VEGF, exhibited a muscle fibre-specific-related mRNA expression at rest in normoxia. However, soleus presented a significantly higher VEGF protein content than vastus lateralis and triceps muscle. Taken together, such findings indicate that there are muscle-specific differences in HIF-1α and VEGF expression within human skeletal muscle at rest in normoxic conditions.

## HIF-1α-independent regulation of VEGF and angiogenesis

Peroxisome proliferator-activated receptor (PPAR)-γ coactivator 1α (PGC-1α) regulates mitochondrial biogenesis in multiple cell types through coactivation of key transcription factors including nuclear respiratory factors (NRF-1 and NRF-2), estrogen-related receptor-α (ERRα), Gabpa/b, PPARs, and the thyroid hormone receptor[21] (Fig. 3)[22]. PGC-1α is a mediator of signaling in response

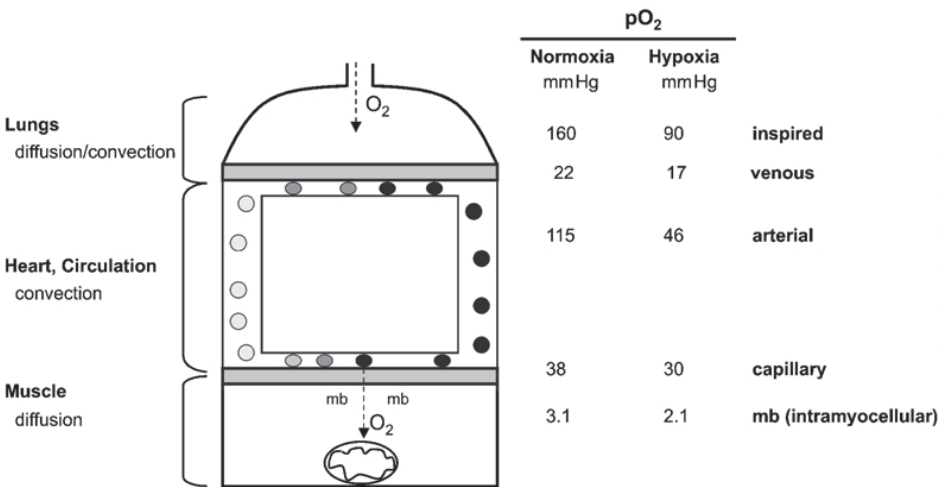


**Fig. 2** The pathway of oxygen[4]. Simplified model of the oxygen transport pathway showing the principal structures and the corresponding partial pressure of oxygen ($pO_2$) in these compartments, during maximal exercise, while breathing normoxic or hypoxic room air. mb, myoglobin. The data are derived from Richardson et al.[14]

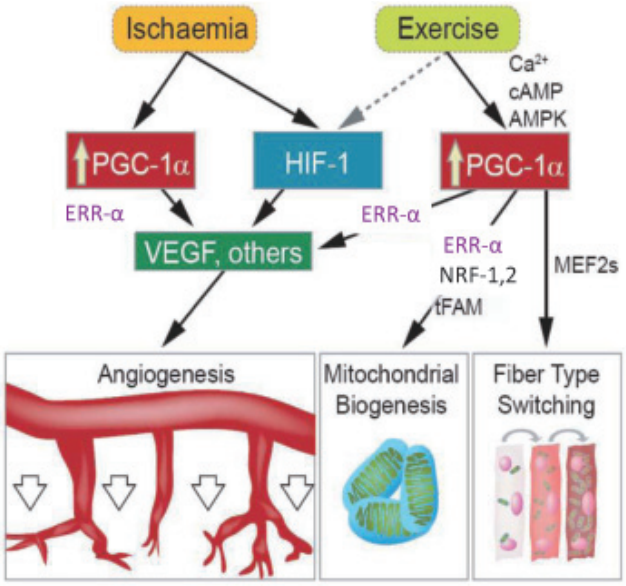


**Fig. 3** PGC-1α regulates expression of VEGF through coactivation of ERR-α[22]. Speculative model for the role of PGC-1α in the regulation of angiogenesis during exercise and in response to ischaemia. AMPK, AMP-activated protein kinase; tFAM, mitochondrial transcription factor A.

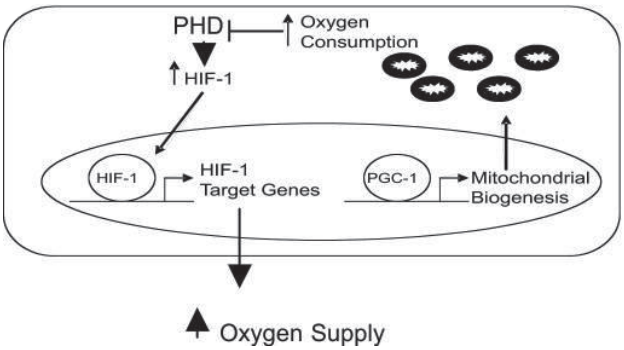


**Fig. 4** Schematic representation of HIF target gene expression by PGC-1α[21]. PGC-1α expression results in mitochondrial biogenesis and increased oxygen consumption. The resultant drop in intracellular $pO_2$ levels leads to decreased HIF hydroxylase activity and HIF stabilization with resultant gene expression that facilitates an increase in oxygen supply. PHD, prolyl hydroxylase.

to deprivation of nutrients and oxygen, and it powerfully regulates VEGF and other angiogenic factors to elicit neovascularization *in vivo*. The regulation of VEGF in response to hypoxia is thought to be mediated primarily through the well-known HIF factors[1]. Surprisingly, the novel PGC-1α/ERR-α pathway (Fig. 3)[22] is apparently independent of the HIF pathway. PGC-1α$^{-/-}$ mice are viable, suggesting that PGC-1α is not essential in embryonic vascularization[22]. Angiogenesis in the adult occurs in both physiological and pathological contexts[23]. The robust induction of vascularization by PGC-1α, and its critical function in the response to limb ischaemia, strongly implicate PGC-1α in the angiogenic response to ischaemia, providing protection against further ischaemic insults[22].

On the other hand, PGC-1α is coupled to HIF signaling through the regulation of intracellular oxygen availability, allowing cells and tissues to match increased oxygen demand after mitochondrial biogenesis with increased oxygen supply, because of intracellular hypoxia (Fig. 4)[21]. PGC-1α-dependent induction of HIF target genes under physiological oxygen concentrations is not through transcriptional coactivation of HIF or up-regulation of HIF-1α mRNA but through HIF-1α protein stabilization.

Other candidates have been proposed for the HIF-1α-independent regulation of VEGF and angiogenesis. Overexpression of suppressor of cytokine signaling 3 (SOCS3), a well-established negative regulator of signal tranducer and activator of transcription 3 (STAT3), enhances the mRNA expression of downstream targets of STAT3, c-FOS and VEGF despite inhibition of STAT3 phosphorylation. These increases were correlated with enhanced mRNA expression of genes associated with muscle maturation and hypertrophy (Fig. 5)[24]. The mechanism by which SOCS3 may mediate these responses, however, is

unknown and will require further investigation. The decline in the regenerative capacity of skeletal muscle with age may be linked to inefficient STAT3/SOCS3 signaling. Actually, a single bout of maximal leg extension exercise (resistance exercise) markedly increased the STAT3 signaling including the SOCS3 gene in human skeletal muscle, accompanied by significant increases in levels of mRNAs for downstream genes of STAT3, c-FOS, JUNB, c-MYC, and VEGF, probably not via HIF signaling[25]. In addition, the levels of HIF-1 mRNA subunits did not change in response to short-term one-legged exercise training, suggesting no change in HIF-1 mRNA transcript levels in the regulation of training-induced VEGF expression[26].

Increased production of reactive oxygen species (ROS), such as $H_2O_2$, also induces the expression of VEGF A, the prototype VEGF ligand, by a HIF-independent and Sp1-dependent mechanism, in which ligation of VEGF A to VEGF receptor 2 (VEGFR2) results in signal transduction leading to tissue vascularization. Such ligation generates $H_2O_2$ via an NADPH oxidase-dependent mechanism[27]. That the function of one mitogen, VEGF, largely depends on the signaling driven by another mitogen, $H_2O_2$, generates a novel paradigm with major therapeutic implications for a variety of angiogenesis-related disorders[28]. Furthermore, oxygen-glucose deprivation generates ROS in cerebral endothelial cells; and, in turn, induces VEGF signaling via its receptor, Flk-1 (VEGFR2), and activates extracellular signal-regulated kinase (ERK) 1/2. This suggests that VEGF acts via ERK 1/2 through oxidative-stress-dependent mechanisms, showing that ERK 1/2 can be considered a molecular target for stroke therapy[29]. Interestingly, high glucose blunts VEGF response to hypoxia in immortalized rat proximal tubular cells. This effect is mediated by the oxidative stress-regulated HIF-hypoxia-responsible element (HRE) pathway[30].

## p38γ MAPK/PGC-1α signaling regulation by physical exercise and its significance for mitochondrial biogenesis and angiogenesis in skeletal muscle

p38γ mitogen-activated protein kinase (MAPK), but not p38α MAPK or p38β, is required for PGC-1α upregulation in mitochondrial biogenesis and angiogenesis in response to voluntary wheel running and nerve stimulation in mice. None of the p38 MAPK isoforms were required for endurance exercise-induced IIb-to-IIa fiber-type transformation in these mice[31]. Meanwhile, the calcineurin (CaN)/nuclear factor of activated T-cells (NFAT) regulatory axis controls fiber-type transformation in endurance exercise-induced skeletal muscle adaptation[32]. Collectively, endurance exercise on one hand induces activation of the $Ca^{2+}$-dependent CaN-NFAT pathway in control of fiber-type transformation and on the other hand activates p38γ MAPK, which promotes PGC-1α activity and expression in control of mitochondrial biogenesis and angiogenesis[32] (Fig. 6)[31].

In addition, an acute bout of sprinting exercise that increased ROS production mainly through a nonmitochondrial enzyme, xanthine oxidase (XO), stimulated PGC-1α expression and other key proteins in the mitochondrial biogenic pathway, such as NRF-1 and transcription factor A, mitochondrial (Tfam). This nuclear-initiated signaling event was accompanied by activation of p38 MAPK and cAMP response element binding protein (CREB) phosphorylation. Inhibition of XO by allopurinol severely attenuated exercise activation of the PGC-1α signaling pathway, thus providing strong evidence that mitochon-

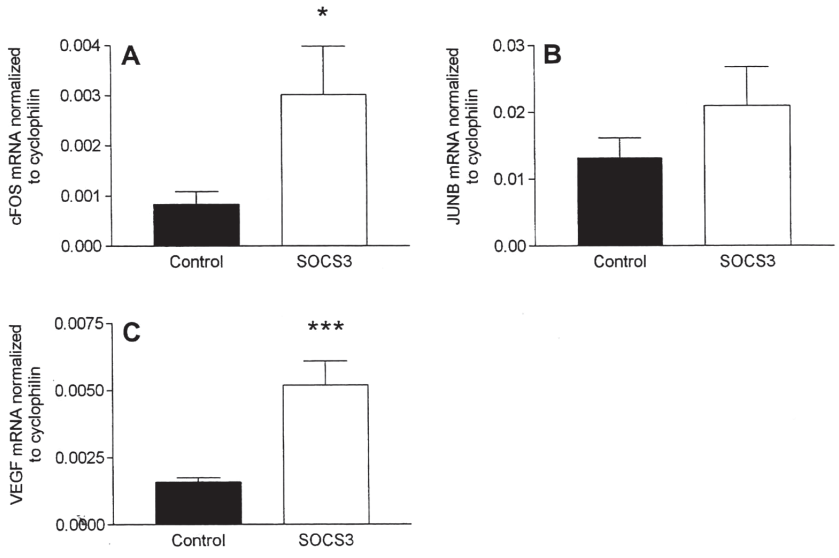


**Fig. 5** SOCS3 increases the expression of STAT3 targets in differentiating myotubes when expression of cFOS (A), JUNB (B) and VEGF (C) mRNA was measured in primary human myoblasts[24]. Values are arbitrary units normalized to the expression levels of the reference gene cyclophilin representing the mean of 6 replicates ± SEM. Closed bars (■) represent without SOCS3, open bars (□) represent with SOCS3 overexpression. Significantly different from respective samples without SOCS3: *p<0.05, ***p<0.001.

drial biogenesis in skeletal muscle is controlled at least in part by a redox-sensitive mechanism[33]. This view is supported by Holloszy[34]. Moreover, stretch-stimulated glucose uptake in skeletal muscle is mediated by a ROS- and p38 MAPK-dependent mechanism that appears to be AMPKα2- and phosphatidylinositol 3-kinase (PI3-K)-independent[35]. This novel signaling mechanism is distinct from canonical contraction- and insulin-stimulated signaling that increases glucose uptake, probably providing an alternative pathway for the development of novel therapeutic drugs to overcome insulin resistance. MAPK activation is also involved in the contraction-induced secretion of VEGF protein from skeletal muscle, which is partially mediated via adenosine acting on $A_{2B}$ adenosine receptors[36].

**Double-faced nature of ROS**

ROS are widely believed to cause or aggravate several human pathologies such as neurodegenerative diseases, cancer, stroke, and many ailments. Antioxidants are assumed to counteract the harmful effects of ROS and therefore prevent or treat oxidative stress-related diseases[37]. On the other hand, there is growing evidence that ROS have beneficial effects. This dual nature of ROS means that ROS act as intracellular signaling molecules and as defense mechanisms against micro-organisms[38]. For instance, the mechanisms by which ROS and cytosolic $H_2O_2$ levels are involved in the stabilization/activation

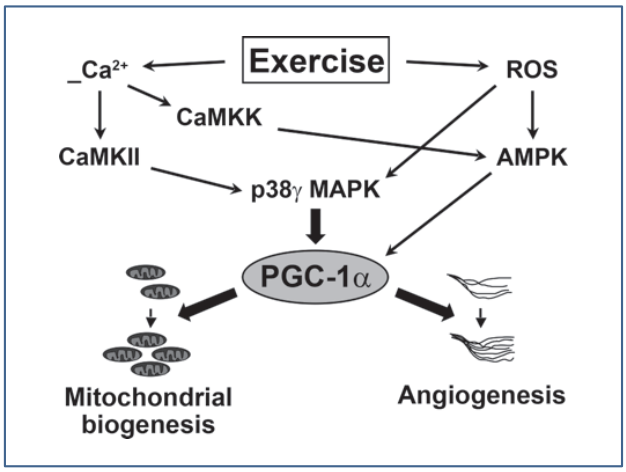


**Fig. 6** Signaling pathways involved in exercise-induced peroxisome-proliferator-activated receptor-γ coactivator-1α (PGC-1α) regulation in skeletal muscle. Current evidence suggests roles for calcineurin (CaN), calmodulin-dependent kinase (CaMK), AMP-activated protein kinase (AMPK), and p38 MAPK in PGC-1α regulation[31]. Thick arrows depict regulatory events required for exercise-mediated induction of PGC-1α and subsequent adaptations that have been confirmed by gene deletion studies in animal models. Thin arrows depict regulatory events that have been associated with PGC-1α regulation, but their requirement for the exercise-dependent induction of PGC-1α awaits further investigation. ROS, reactive oxygen species.

and eventual degradation/silencing of HIF-1α and other redox-sensitive transcription factors, such as MAPK and PI-3K/Akt, are controversially discussed[39].

Mitochondria and mitochondria-derived ROS were required for the stabilization of HIF-1α by MAPK and by exposure of hepatoma cells to 6 h of hypoxia (1.5% $O_2$)[40]. This hypoxic stabilization of HIF-1α in hepatoma cells was blocked by the overexpression of catalase, which catalyses dismutation of $H_2O_2$ into $H_2O$ and $O_2$, and is an inhibitor of the mitochondria superanion channel. Also, HIF-1α and VEGF overexpression in pulmonary artery smooth muscle was induced by $CoCl_2$, which mimics the hypoxic response, via ROS[41]. Such overexpression was inhibited by vitamin C and by the overexpression of GPX and catalase. By contrast, the addition of $H_2O_2$ in the absence of a hypoxic stimulus causes stabilization of HIF-1α[40]. Anoxia, on the other hand, may stabilize HIF-1α essentially through depletion of the co-substrate dioxygen of prolyl hydroxylases, indicating that increases in cytosolic $H_2O_2$ inconsequence of hypoxia-driven ROS production may cause HIF-1α accumulation in hypoxia through reduction of hydroxylation (Fig. 7)[4]. Actually, during the "acute" increase phase of HIF-1α (between 0 and 2 h), 8-hydroxy-2'-deoxyguanosine (8-OHdG) was positively correlated with HIF-1α during sustained hypoxia in humans[42]. Moreover, ROS-activated signaling events involving MAPK and PI-3K/Art have been implied in the modulation of the transcriptional activity of HIF-1α[43]. Further, angiotensin II *in vivo* and *in vitro* up-regulates renal VEGF expression by a mechanism that involves HIF-1 activation and oxidative stress[44].

Thus, it now seems possible that ROS have important roles in the regulation of cell signaling, although these substances are potentially cell damaging. For example, there appears to be a potential feedback loop in which PGC-1α regulates antioxidant mechanisms via regulation of mitochondrial respiration and ROS. In turn, ROS might regulate antioxidant defense genes through activation of redox-sensitive transcription factors, supporting the view that ROS are important signaling molecules in adaptation to exercise (Fig. 8)[45]. Whereas increasing evidence suggests that mitochondria play a less important role in oxidant production in contracting skeletal muscles than was previously predicted, and the primary site of contraction-induced ROS production in muscle fibers remains unclear[46,47], PGC-1α is transiently induced by acute exercise[34,48]. This induction has been suggested to occur in response to altered energy demands and because of PGC-1α interacting with the metabolic enzyme AMPK[49]. PGC-1α has also been proposed to be a key mediator of long-term adaptation to exercise[49]. Indeed, basal levels of PGC-1α gene expression increased approximately two-fold after a period of endurance training in humans[50].

Intriguingly, in conflict with the free radical theory of aging (FRTA)[51], longevity and health-promoting effects of caloric restriction and specifically reduced glucose

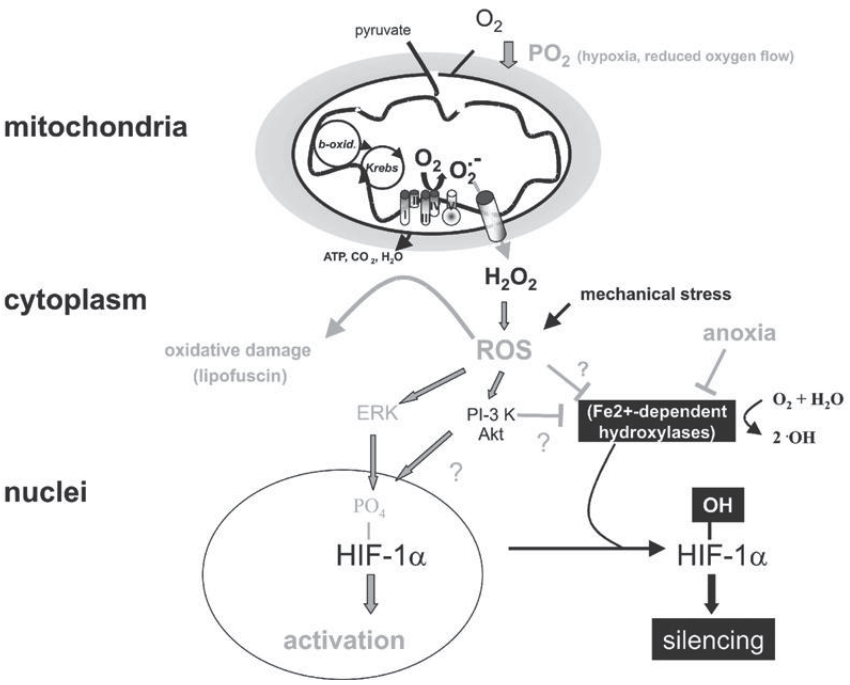


**Fig. 7** Targets of mitochondrial ROS production[4]. Incomplete reduction of $O_2$ during normal metabolic conversion of pyruvate in mitochondria gives rise to a low level of superoxide anion ($O_2^{\cdot-}$). Exposure of cells to hypoxia increases the aberrant production of $O_2^{\cdot-}$ at the mitochondrial electron chain complex III. Catalyzed or spontaneous dismutation of the unstable superanion and export via anion channels enhances the concentration of cytosolic $H_2O_2$ and othe reactive oxygen species (ROS). Increased ROS may increase the level of oxidatively damaged lipids (lipofuscin) or activate downstream redox-sensitive signal transduction events. For example ROS stabilize HIF-1α possibly by interfering with the activity of $Fe^{2+}$-dependent proline hydroxylases. ROS may also activate the MAPK or PI-3K/Akt pathway, which enhances the transcriptional activity of HIF-1α through its phosphorylation. Lastly, mechanical stress may also increase ROS production that may influence HIF-1α activation.

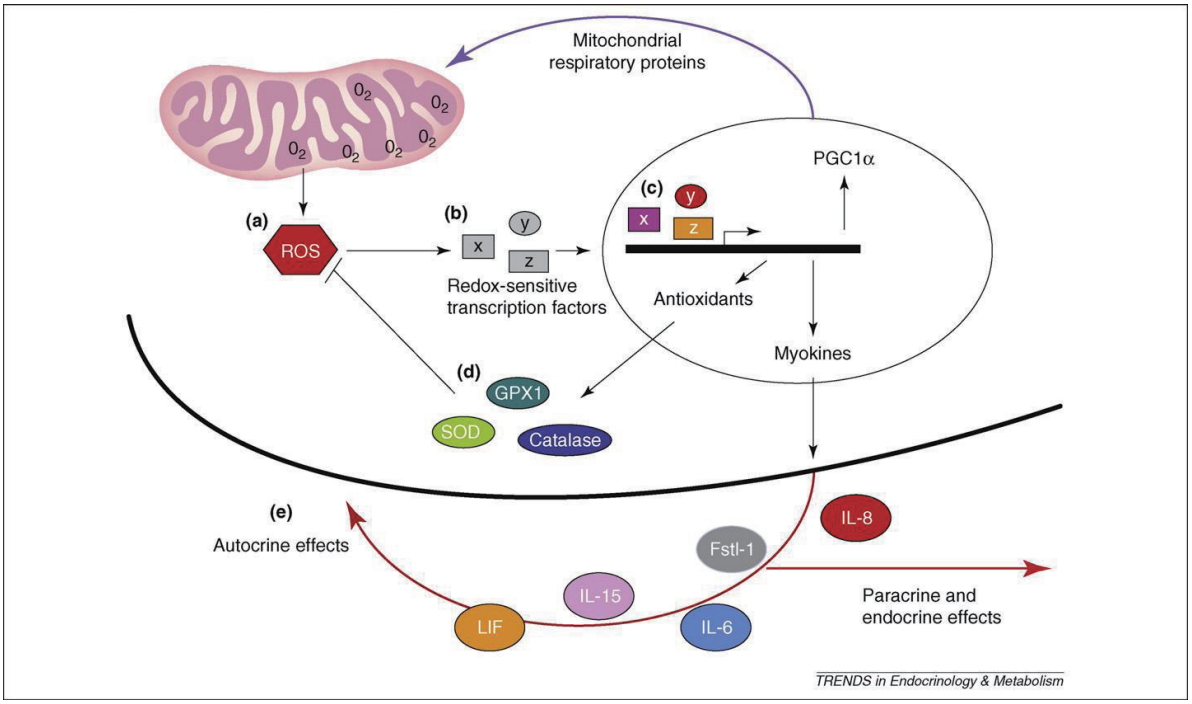


**Fig. 8** Proposed model of signaling activation by ROS in skeletal muscle in response to exercise[45]. (a) Reactive oxygen species (ROS) are produced from mitochondrial respiration by a leakage of electron from the electron-transport chain to oxygen. This process increases during exercise as a consequence of increased mitochondrial activity. (b) ROS have the potential to regulate cell signaling by affecting redox-sensitive transcription factors (here assigned x, y and z), inducing PGC-1α, antioxidant defense mechanisms and myokines. (c) PGC-1α activates gene involved in mitochondrial respiration, enabling increased mitochondrial activity, whereas (d) endogenous antioxidants such as superoxide dismutase (SOD), glutathione peroxidase-1 (GPX1) and catalase buffer the increased amount of ROS. (e) Myokines act in autocrine, paracrine or endocrine fashion to stimulate hypertrophy (IL-6, LIF and IL-15) or angiogenesis (IL-8 and Fstl-1).

metabolism may be due to increased formation of ROS within the mitochondria causing an adaptive response that culminates in subsequently increased stress resistance assumed to ultimately cause a long-term reduction of oxidative stress. This adaptive response is known as mitochondrial hormesis or mitohormesis[52]. Molecular mediators of endogenous ROS defense (SOD 1 and 2 and GPX) are also induced by exercise, and this effect is blocked by antioxidant supplementation[53]. Consistent with the concept of mitohormesis, exercise-induced oxidative stress ameliorates insulin resistance and causes an adaptive response promoting endogeneous antioxidant defense capacity. As expected or unexpectedly, supplementation with antioxidants may preclude these health-promoting effects of exercise in humans. Taken together, physical exercise induces numerous molecular regulators of insulin sensitivity and antioxidant defense, most of which are almost completely inhibited by antioxidant pretreatment in healthy young men[52,54] (Fig. 9)[53].

Furthermore, lactate elevation is a ubiquitous characteristic of tumors and wounds. ROS production by Fenton-like reactions from lactate metabolism by stem/progenitor cells (SPCs) accelerates further SPC recruitment and differentiation through thioredoxin 1-mediated elevations in HIF-1 levels and the subsequent synthesis of HIF-1-dependent growth factors, such as VEGF and stromal cell-derived factor[55].

### Effect of exercise on HIF and VEGF signaling

The study on acute exercise by Ameln et al.[56] is the first to show that several components of the HIF-1 pathway, involving VEGF and EPO, are activated in response to acute changes in oxygen demand in healthy human skeletal muscle. This is due to a concurrent decrease in VHL tumor suppressor protein levels, suggesting that oxygen sensitive pathways could be relevant for adaptation to physical activity by increasing capillary growth in human skeletal muscle. Such findings support the general importance of the HIF pathway (Fig. 10)[56]. VEGF mRNA is further increased when blood flow to the exercising leg is restricted.

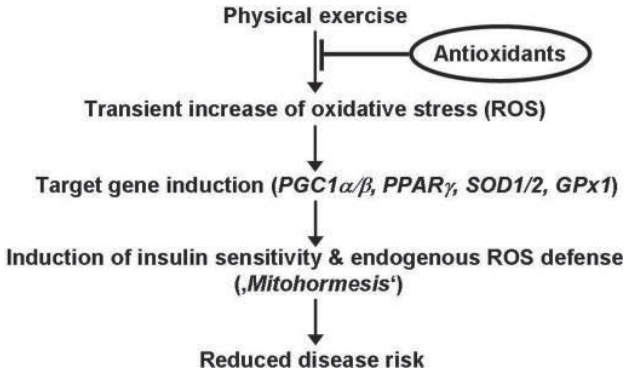


**Fig. 9** Mitohormesis links physical exercise and subsequent formation of reactive oxygen species to insulin sensitivity and antioxidant defense[53]. Physical exercise exerts ameliorating effects on insulin resistance by increasing mitochondrial formation of reactive oxygen species in skeletal muscle to induce expression of PGC-1α, PGC-1β, and PPARγ as inducers of insulin sensitivity, as well as SODs 1 and 2 and glutathione peroxidase 1, key enzymes of ROS defense. Notably, by blocking exercise-dependent formation of ROS due to ingestion of antioxidant supplements, health promoting effects of physical exercise are abolished, and physical exercise fails to promote insulin sensitivity and antioxidant defense in the presence of vitamin C and vitamin E.

Also, several studies have revealed increased levels of the HIF-1 pathway in human skeletal muscle following acute exercise[57,58]. The positive response of mRNAs for HIF-1α and HIF-2α by acute exercise, however, is blunted with training[58]. Moreover, a positive correlation was found between exercise-induced changes in VEGF mRNA on one hand, and changes in HIF-1α mRNA, HIF-1β mRNA, and lactate on the other; while no significant differences between the restricted and nonrestricted groups were observed[57], unlike the study of Ameln et al.[56]. This lack of a further increase in VEGF mRNA when flow restriction was "added" may be explained by the smaller further reduction in oxygen saturation and oxygen tension compared with the rest-to-exercise transition, even if this difference was large enough to induce a greater lactate concentration increase in the restricted condition. Another explanation could be that, even if there was no significant VEGF mRNA difference before exercise between nonrestricted and restricted conditions, a strong influence of the preexercise value of VEGF mRNA on the exercise-induced increase makes a difference between the two conditions more difficult to detect.

Exercise induces several pathways that are known to be important for regulating angiogenesis. VEGF is critical for basal and activity-induced regulation of skeletal muscle capillarization; whereas the importance of other growth factor pathways remains to be elucidated. Although several signaling pathways have been identified (Fig. 11)[59], significant work remains on understanding the intracellular signaling pathways and transcription factors involved in basal and exercise-induced angiogenesis.

For example, in addition to AMPK, exercise activates several signaling pathways that may be the link between metabolism and capillarization including calcium ($Ca^{2+}$)-regulated pathways[59]. Large but transient increases in intracellular $Ca^{2+}$ occur during exercise as a result of neural activation and muscle cell depolarization. $Ca^{2+}$ is intimately involved in actin-myosin cross-bridge formation and is responsible in part for exercise-induced improvements in insulin sensitivity that occur in part through increases in glucose transporter 4. Increasing intracellular $Ca^{2+}$ leads to the activation of several downstream signaling proteins including calmodulin-dependent kinase (CaMK) and CaN, possibly resulting in increased expression of VEGF mRNA in primary human myotubes *in*

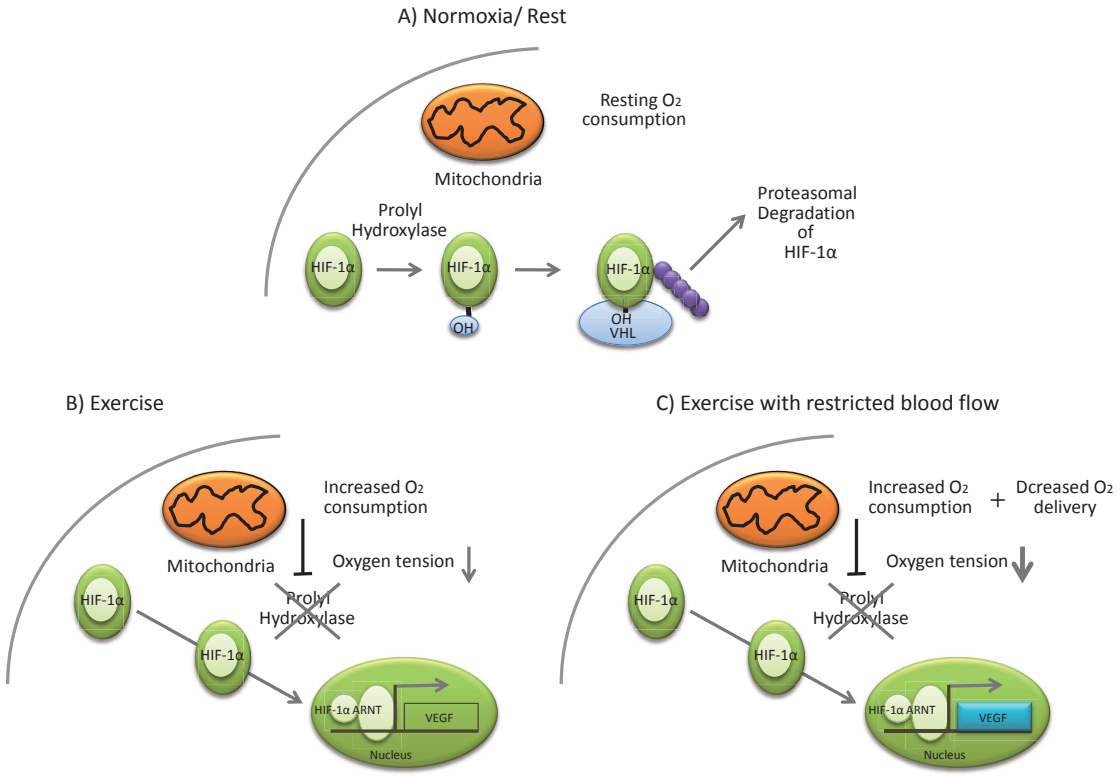


**Fig. 10** HIF-1 activation in exercising human skeletal muscle[56]. In normoxia/rest (A), low HIF-1α levels were found, lending support to the idea that HIF-1α is hydroxylated by a prolyl hydroxylase recognized by von Hippel-Lindau tumor suppressor protein (VHL), a ubiquitin-protein ligase, and targeted for degradation by the proteasome. Exercise (B) increases oxygen consumption and reduces oxygen tension to levels that inhibit prolyl hydroxylase, resulting in accumulation of the HIF-1α prptein and translocation into the nucleus. In the nucleus, HIF-1α and ARNT (HIF-1β) dimerized and activated target genes such as VEGF and erythropoietin (EPO). No further activation of HIF-1 was observed when oxygen delivery to the exercising muscle was reduced (C). mRNA levels for VEGF (but not EPO) were significantly higher when blood flow to the exercising leg was restricted.

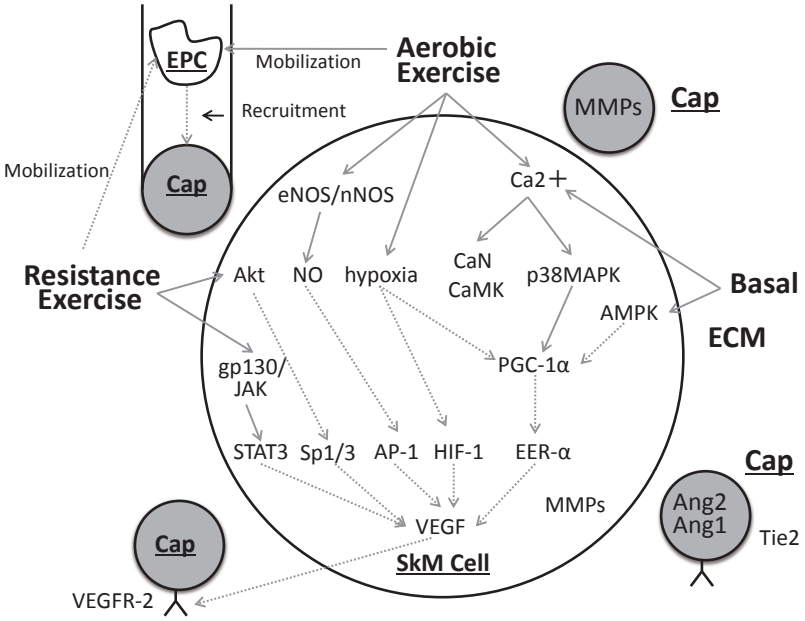


**Fig. 11** Proposed model including intracellular signaling and growth factor regulation in skeletal muscle (SkM) cells, capillaries lined with endothelial cells (Caps), extracellular matrix (ECM), and endothelial progenitor cells (EPCs)[59]. AMPK indicates 5'-adenosine monophosphate-activated protein kinase; Ang1 and 2, angiopoietins 1 and 2; Ap-1, activator protein 1; CaMK, calmodulin-dependent kinase; CaN, calcineurin; eNOS, endothelial nitric oxide synthase; ERR-α, estrogen-related receptor-α; HIF-1, hypoxia-inducible factor; gp 130/JAK, glycoprotein 130/Janus family of tyrosine kinases; MMPs, matrix metalloproteinases; nNOS, neuronal NOS; NO, nitric oxide; NOS, nitric oxide synthase; p38 MAPK, p38 mitogen activated protein kinase; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1α; STAT3, signal transducers and activator of transcription; Tie2, Tie receptor for Ang1 and Ang2; VEGF, vascular endothelial growth factor; VEGFR-2, VEGF receptor 2. Solid lines (−) are established pathways. Dashed lines ( - - ) are hypothesized pathways.

*vitro*, suggesting that calcium may be involved in muscle VEGF regulation[59]; although much more work needs to be done before these studies are finalized. In addition, PPAR-β, which is also known as PPARδ and is involved in muscle development and metabolism, increases VEGF and promotes muscle angiogenesis through a CaN-dependent pathway[60].

Moreover, nitric oxide (NO) is involved in muscle VEGF regulation[61] (Fig. 11)[59]. NO is generated by NO synthase (NOS) and is produced in muscle by neuronal NOS (nNOS) and in endothelial cells by endothelial NOS (eNOS). nNOS production of NO regulates, in part, muscle mitochondrial respiration, whereas eNOS production of NO is involved in blood flow regulation. Disrupting normal NO production (via L-NAME) eliminates the increase in collateral blood flow induced by training, but does not disturb the increase in muscle capillarity within the active muscle. Similarly, inhibiting VEGFR kinase activity eliminates the increase in collateral-dependent blood flow, and lessens, but does not eliminate, angiogenesis in the calf muscle, illustrating distinctions between the processes influencing angiogenesis and arteriogenesis[61].

In general, the effects of endurance training on the activity of the HIF pathway in human skeletal muscle under hypoxic conditions appear to be definitely higher than those under normoxic conditions[62-64]; although there are several exceptions[65,66], indicating that combining hypoxia with exercise training appears to improve some aspects of muscle $O_2$ transport and/or metabolism[64]. Although there were no significant changes in the levels of mRNAs for HIF-1α or VEGF in human skeletal muscle after endurance training under normoxic conditions, the changes in HIF-1α mRNA expression correlated well with those in VEGF mRNA expression (Fig. 12)[67], suggesting that HIF-1α influences the training-induced VEGF gene expression or alternatively that HIF-1α and VEGF expression is co-regulated at the transcriptional level in human skeletal muscle. Taken together, it is envisioned that the cumulative effects of transient changes in transcription during recovery from successive bouts of exercise may represent the underlying kinetic basis for the cellular adaptations associated with endurance training. Furthermore, no plasma VEGF concentrations in overweight men aged 50-60 years were affected by long-term endurance exercise under normoxic conditions[68]. Likewise, low or high intensity resistance exercise did not significantly alter serum VEGF concentrations in humans[69].

## Future directions

As already stated, HIF-1-mediated pathways have multiple functions. Recently, it has been reported that loss of VHL-1 in C. elegans significantly increases lifespan and enhances resistance to polyglutamine and amyloid β toxicity[70]. Deletion of HIF-1 is epistatic to VHL-1, indicating that HIF-1 acts downstream of VHL-1 to modulate aging and proteotoxicity. VHL-1 and HIF-1 control longevity by a mechanism distinct from both dietary restriction and insulin/IGF-1-like signaling[70,71]. Moreover, ROS are increased in respiration mutants of C. elegans and mild increases in ROS can stimulate HIF-1 to activate gene expression and promote longevity, suggesting that HIF-1 links respiratory stress in the mitochondria to a nuclear transcriptional response that promotes longevity[72]. The question whether this is also true for humans, however, cannot be answered at present.

On the other hand, the depression of HIF-1-mediated pathways appears to be a "natural" part of aging. VEGF, VEGFR1, VEGFR2 mRNA and protein levels are reduced in the hearts of aged (23-month-old) sedentary rats compared to young (4-month-old) sedentary rats or aged rats subjected to a swimming regimen for 8 weeks[73]. Cardiac capillary density mirrored the changes in VEGF expression with age and exercise. In humans, similar studies have shown depressed capillarization and lower VEGF protein in the skeletal muscles of elderly humans compared to young humans[74,75]. In elderly patients with stable coronary disease or peripheral vascular disease subjected to exercise to an ischaemic threshold, the number of endothelial progenitor cells (EPCs), regulated by HIF-1, and plasma VEGF are increased[76]. Hence, exercise by stimulating HIF-1 signaling, may maintain vascular youth[77,78]. Moreover, it should be emphasized that a cheap and ready therapy to augment HIF-1-mediated pathways is exercise[78].

On the contrary, age-associated increases in HIF-1α and VEGF levels in rat skeletal muscle were observed, possibly due to mitocondrially increased generation of ROS with aging[79]. Unexpectedly, exercise training decreased levels of both HIF-1α and VEGF in aged rats, which appears to run contradictory to the understanding that HIF-1α mediates exercise-induced oxidative adaptation to

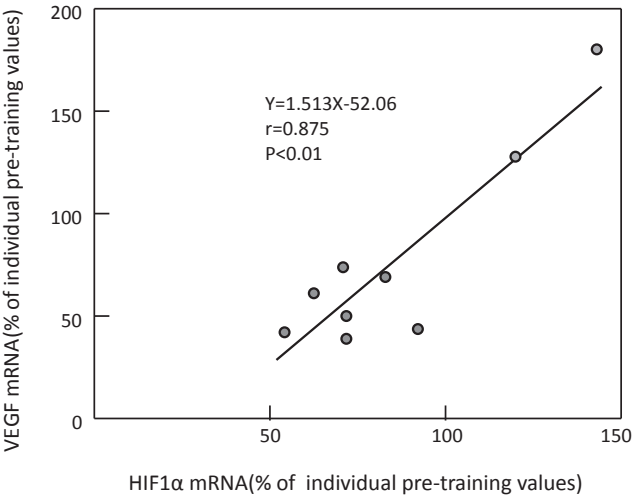


**Fig. 12** Correlation between HIF-1α and VEGF mRNA expression in human skeletal muscle after endurance training[67].

skeletal muscle[80]. Thus, the precise relationship of VEGF, exercise, aging, and ROS and the HIF-1 pathway needs further study.

Lastly, the study of the HIF and VEGF signaling (via the ROS production) appears to be shifting from terra incognita to terra firma – ensuring some promising breakthroughs in the near future.

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J Phys Fitness Sports Med, **1(1)**: 133-137 (2012)

**JPFSM:** ***Short Review Article***

# Exercise, nutrition and iron status

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Received: February 15, 2012 / Accepted: February 20, 2012

***Abstract*** Iron deficiency is still a problem in developing countries as well as developed countries. Moreover, an athletic population has a high rate of iron deficiency anemia; most of whom participate in aerobic exercise. Therefore, most studies which have been conducted to investigate the effect of exercise on iron status have used aerobic exercise. A considerable number of studies suggest that aerobic exercise has harmful effects on the iron levels in the body. Therefore, most of the studies on improving iron deficiency focus on the effect of nutrition. However, mild resistance exercise improves iron status in the body. These results suggest the possibility of a difference in the effect of different types of exercise on iron status. Exercise would be economically advantageous as a measure to improve iron deficiency in developing countries that have a high rate of iron deficiency. Future studies might thus be needed to clarify the relationship between iron status and physical activity.

***Keywords*** : iron deficiency, exercise, hemoglobin, heme synthesis, nutrition, anemia

## Introduction

Iron deficiency is one of the most common nutritional problems in the world. The World Health Organization (WHO) estimated the prevalence of iron deficiency to be 15-20% of the world's population[1)]. Iron deficiency is defined as a low level of internally stored iron and an insufficient supply of iron to various tissues.

Iron deficiency is thought to be caused by low iron intake, some relevant diseases, and, in women, blood loss by menstruation. Anemia (iron deficiency anemia) results from decreasing hematopoiesis in the hematopoietic tissues due to iron deficiency. Iron deficiency in tissues occurs either quickly or slowly depending on the balance between iron intake (or stockpile) and iron requirement. The developmental rate of iron deficiency in individual tissues and cell organelles depends on the turnover rate of iron-containing proteins.

Iron is associated with several metabolic processes, including mitochondrial electron transport, neurotransmitter synthesis, protein synthesis, organogenesis, and others. Therefore, iron deficiency results in several deleterious effects including decreases in work performance, immune function, sympathetic, endocrinological metabolism, and thermoregulatory performance[2-5)]. In addition, the reduction in hemoglobin due to iron deficiency causes changes in physical capacity through the decrease of an oxygen transporter in muscle. The content of iron-sulfur and cytochrome in mitochondria and the oxidative capacity of mitochondria are also decreased by iron deficiency. In short, the decreased exercise capacity occurs in association with the decrease in oxygen-carrying capacity, oxygen diffusing capacity in tissue and oxidizing capability in muscle. There is a change in the metabolic function associated with non-anemia iron deficiency[6)]. A sufficient level of iron in tissue as well as hemoglobin has therefore been reported to be important to enhance maximal oxygen uptake[7,8)].

There has been a considerable amount of research on the effect of exercise or nutrition on iron status. Most of the studies on improving iron deficiency focus on the effect of nutrition. Few studies have so far investigated the effect of exercise on the prevention and/or improvement of iron deficiency. Therefore, this short review will demonstrate the effect of the type of exercise and the combination of exercise and nutrition on iron status.

## Effect of exercise on iron status

Previous studies have shown that exercise itself can change the iron status in the body. Studies of athletes suggest that athletes tend to have a low serum ferritin level[9)]. These results are seen especially in long distance runners. Iron deficient anemia is a type of malnutrition that is frequently seen in female athletes. The primary cause is a lack of iron in the diet[10,11)]. The requirement for iron in a high-performance athlete is exacerbated by profuse perspiration (containing decidual epidermal cells), reduced fractional absorption of iron from the digestive tract, erythrocyte destruction by physical impact on the feet and

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iron hypermetabolism by erythrocyte destruction. Many of these studies investigated the impact of aerobic exercise. Studies on the effect of resistance exercise suggest a possible difference in the effect of exercise on iron status associated with the type of exercise (aerobic exercise vs. resistance exercise).

***Aerobic exercise and iron status.*** Several studies have reported that decreases in hematocrit, hemoglobin, and serum iron and an increase in erythrocyte fragility may occur in individuals that participate in extreme aerobic exercise[12-15]. Several investigators have proposed mechanisms by which iron balance could be affected by intense physical exercise[16-18]. Explanations include increased gastrointestinal blood loss after running and hematuria as a result of erythrocyte rupture within the foot during running. The possibility of increased red cell turnover in athletes is supported by the ferrokinetic measurements conducted by Ehn et al.[19]. They demonstrated that the whole-body loss of radioactive iron occurred 20% faster in female athletes than in non-athletes, and both were faster than that in adult men. In addition, they reported that hemoglobin and serum iron were normal, while bone marrow showed non-anemic iron deficiency. The red cell turnover of iron deficient rats with exercise was increased in comparison to that in sedentary rats[20].

On the other hand, aerobic exercise improves or mitigates deteriorated iron status in iron deficient rats. Perkkio et al. reported that the hemoglobin concentration, endurance capacity and $\dot{V}O_2$max of iron deficient rats are significantly increased by aerobic exercise (treadmill) in comparison to that in sedentary rats[21]. However, the hemoglobin concentration of iron sufficient rats was not decreased by exercise in comparison to that in sedentary rats. Willis et al. reported that the hemoglobin concentration of iron deficient rats was significantly increased by aerobic exercise (treadmill) in comparison to that in sedentary rats[22]. Gagne et al. observed that the hemoglobin concentration and hematocrit were not decreased while the stainable bone marrow iron was lowered significantly by exercise[23]. They suggested that this phenomenon was most likely due to the increase in iron turnover as well as the rate of hemoglobin synthesis and release from cells induced by exercise. Qian et al. reported that the rate of hemoglobin synthesis and the amount of iron uptake in the bone marrow erythroblasts were increased in the strenuously exercised rats (swimming), while the iron content of the liver, spleen, kidney and heart were decreased[24]. The iron deficiency in tissues is thought to be due to increased iron acquired by bone marrow cells and used for increased hemoglobin synthesis. Exercise could lead to a shift of iron from storage sites to bone marrow cells for increased hemoglobin synthesis. Similarly, lower iron stores were observed in the tissue of the exercised rats in comparison to sedentary rats. Strause et al. demonstrated that exercised rats had less total iron in the liver and spleen than sedentary rats[25]. Ruckman et al. observed the hemoglobin of trained rats was increased in comparison to sedentary rats[26]. However they suggested that there was an overall trend toward iron depletion in the liver and spleen of the exercised rats and that trend of decreased iron level in organs could be related to increased hemoglobin levels.

***Resistance exercise and iron status.*** Few studies have investigated the effect of resistance exercise on iron metabolism in comparison to aerobic exercise. Mild resistance exercise improves the iron status in young women with non-anemic iron deficiency without iron supplementation[27]. The levels of serum ferritin, hemoglobin, number of red blood cells and total iron binding capacity increased significantly after 12 weeks of resistance exercise (dumbbell exercise) in young women with non-anemic iron deficiency. These findings revealed that daily mild resistance exercise can improve non-anemic iron deficiency and prevent iron deficient anemia. Serum iron levels did not increase. Mild exercise did not increase iron absorption from the gastrointestinal tract[28]. Therefore, these observations suggest the possibility that dumbbell exercise did not enhance iron absorption, but it did improve the iron status in the body due to an increased expression of iron binding proteins.

The effect of resistance exercise on iron status was investigated using voluntary resistance training (climbing) equipment developed for rats. An experiment with severely iron deficient rats observed that the hemoglobin concentration of rats exercised for 8 weeks significantly increased in comparison to sedentary rats[29,30]. Moreover, as shown in Figure 1, resistance exercise (climbing) was associated with a greater increase in the hemoglobin concentration in comparison to aerobic exercise (swim-

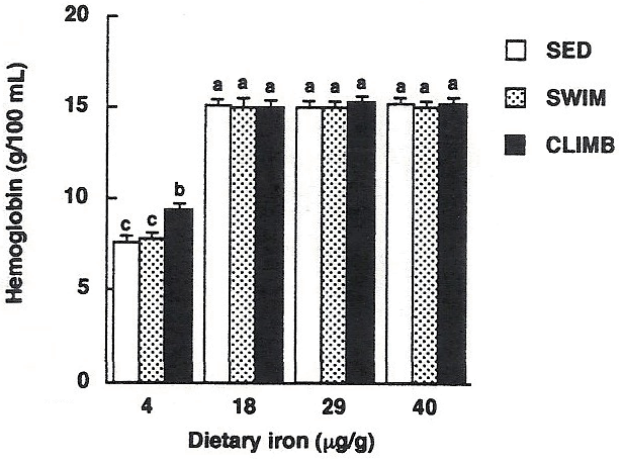


**Fig. 1** Effects of swimming or climbing exercise on hemoglobin concentration in rats receiving 4, 18, 29, and 40 mg Fe/kg diet for 8 wk. Values are means and SE for 6 rats. Means with different superscripts are significantly different at $p<0.05$, determined by ANOVA and Fisher's PLSD test. SED, sedentary; SWIM, swimming exercise; CLIMB, climbing exercise.

ming). The hemoglobin concentration in moderately iron deficient rats tended to be higher in the rats who participated in climbing exercise for 3 weeks in comparison to sedentary rats[31]. Ruckman et al. suggested that decreases in the iron levels in the liver and spleen might be associated with an increase in hemoglobin and that exercise influences the distribution and reuse of iron in the body[26]. Resistance exercise does not decrease the iron content in the liver, spleen, kidney and heart, while iron in the flexor hallucis longus (FHL) of rats trained by resistance exercise significantly increases in comparison to sedentary rats[31]. Iron obtained from metabolism, such as the degradation of senescent erythrocytes in addition to dietary iron can be utilized for the synthesis of hemoglobin, myoglobin, and cytochrome. It is therefore plausible that exercise may facilitate the recycling of iron in the body as well as influencing iron distribution between tissues.

**Effect of exercise on heme synthesis**

δ-aminolevulinic acid dehydratase (ALAD) and aminolevulinic acid synthase (ALAS), which are the rate-limiting enzymes in hemoglobin synthesis are often measured to examine the impact of exercise.

Holloszy et al. reported that acute running exercise in rats that did not perform habitual running exercise, led to a two-fold increase in ALAS activity in the red portion of the vastus lateralis muscle in comparison to control rats at 17h (hours) after exercise, while the same activity returned to a level equal to the control by 40h after exercise[32]. Abraham et al. reported that ALAS activity in the ventricles of rats not participating in regular exercise increased after a single bout of running exercise, whereas ALAS activity in rats participating in habitual running exercise was not changed by acute exercise[33].

Bone marrow ALAD activity in rats that perform habitual climbing exercise was increased by a single exercise bout[34]. In addition, the time-dependent changes in the ALAD activity of the bone marrow were measured after resistance exercise as an index of heme biosynthesis capacity. Bone marrow ALAD activity was increased post-exercise, but decreased over time during the post-exercise period[34].

Holloszy et al. reported that ALAS activity in the red portion of the vastus lateralis muscle is increased by treadmill running for 3 months[32]. Bone marrow ALAD activity in iron deficient rats increased after 3 weeks of climbing exercise in comparison to sedentary rats (Fig. 2)[31,35]. In addition, the bone marrow ALAD activity was not increased by swimming exercise in iron deficient rats that performed climbing exercise or swimming exercise for 3 weeks; whereas it was increased by climbing exercise[35]. This increase in ALAD activity appears to be associated with a greater increase in hemoglobin concentration in climbing-exercised rats than in swimming-exercised rats.

Plasma iron is used for hemoglobin synthesis[36]. Baltaci et al. reported that the plasma iron concentration was increased 24 h after an acute swimming exercise that lasted for 30 min[37]. Both the bone marrow ALAD activity and plasma iron concentration were higher post-exercise than pre-exercise[34]. The hemoglobin concentration of iron deficient rats trained by resistance exercise increased in comparison to sedentary or swimming-trained rats[29,30]. Therefore, these findings suggest that resistance exercise is superior for improving the iron status in comparison to aerobic exercise because it leads to concomitant increases in both the plasma iron concentration and bone marrow ALAD activity after resistance exercise which, thus, facilitates hemoglobin synthesis in iron deficient rats engaged in resistance training.

**Nutrition**

The absorption of heme iron is higher than non-heme iron. Protein from a meat factor source promotes iron absorption, but not all protein has this effect. Moreover, a meat factor increases the absorption of non-heme iron twofold; yet not all animal protein has this effect[38]. However, protein is a component of hemoglobin and myoglobin involved in the storage and transportation of iron, respectively; and the intake of a high protein diet is often recommended to prevent anemia. In fact, previous studies reported that a diet low in protein leads to anemia[39,40]. A study investigated whether a high protein diet could enhance the anemia mitigating effects of resistance exercise in rats fed a moderately iron deficient diet. The results showed that a high protein diet has no effect on bone

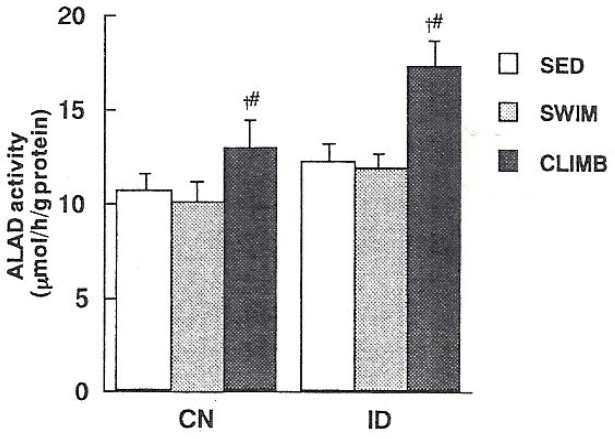


**Fig. 2** Effects of exercise and iron deficiency on bone marrow δ-aminolevulinic acid dehydratase activity in rats. Values are means and SE for 4 rats. †Statistically significant difference from the sedentary-group value. #Statistically significant difference from the swimming exercise-group value ($p < 0.05$, ANOVA and Fisher's PLSD test). ANOVA indicated significant ($p < 0.05$) main effects of exercise. CN, control; ID, iron deficiency; SED, sedentary; SWIM, swimming exercise; CLIMB, climbing exercise; ALAD, δ-aminolevulinic acid dehydratase.

marrow ALAD activity and hemoglobin concentration[41]. However, the iron content in the FHL and heart increased in comparison to rats fed a normal protein diet. Ruckman et al. reported that the hemoglobin concentration increases while the iron content in the liver and spleen decreases with swimming exercise[26]. They then suggested that the decreases of iron in the liver and spleen might be associated with an increase in hemoglobin and that exercise influences the distribution and reuse of iron in the body[26]. Strause et al. suggest that exercise changes tissue iron distribution toward tissues with high oxygen consumption[25]. The higher iron content in the FHL and heart of rats fed a high protein diet is thought to be due to the high protein diet because both groups performed exercise training. There is a possibility that ALAD activity in the FHL and heart is enhanced by a high protein diet. However, this possibility was not confirmed because only bone marrow ALAD activity was measured. That study suggested that a high protein diet does not have any significant effect on increasing hemoglobin synthesis because the bone marrow activity that has a direct relationship with hemoglobin showed no difference between a high protein diet and a normal protein diet. However, the effect of a high protein diet on ALAD activity in tissues other than bone marrow was unclear. Further studies are required to elucidate the effect of a high protein diet, and the additive and/or synergetic effect of a high protein diet and resistance exercise on iron status.

Resistance exercise enhances skeletal muscle protein synthesis[42]. In addition, skeletal muscle protein synthesis is higher when post-exercise nutrition is provided soon after exercise in comparison to when it is provided later[43-46]. Therefore, the effect of post-exercise meal timing on iron status was investigated in rats fed either post-exercise meal soon after exercise or 4h after exercise[34]. The hemoglobin concentration and bone marrow ALAD activity did not differ between the groups after a 3-week study period, thus suggesting that the post-exercise meal timing does not have any significant effect on hemoglobin synthesis, unlike skeletal muscle protein synthesis.

Iron supplements are widely used by people who do not exercise regularly as well as by athletes to prevent anemia. A variety of products are marketed to improve iron balance. Brigham et al. reported that low-dose administration of supplements containing ferrous sulfate (39 mg Fe/day) for 5 weeks prevented the decrease in serum ferritin in competitive female swimmers[47]. Hinton et al. reported an increase in the serum ferritin level; while improved endurance performance was observed in non-anemic women that received 100 mg of ferrous sulfate for 6 weeks[48]. Kang et al. reported that serum ferritin was significantly increased and a reduction in hemoglobin was prevented in elite young female soccer players given 40 mg/day iron supplementation for 4 weeks[49]. The dosage of iron used in the above studies was low. Therefore, it is suggested that iron storage is effective even at low doses. Iron is an essential trace element for biological functions. However, excess intake causes gastrointestinal problems such as nausea, vomiting and diarrhea. In addition, consumption of iron in large amounts for the long term has potential health risks. One should therefore be cautious when using iron supplements.

## Conclusion

Iron is an essential trace element for biological functions such as oxygen transport and enzymatic activity. However, excess iron can also be toxic to cells since it is associated with free radical production. Therefore, the intravital iron balance must be deftly regulated. Intravital iron metabolism forms a semi-closed circle of absorption, storage and recycling of iron. The recycling capability of iron may be enhanced by resistance exercise. Such exercise may therefore be a potentially effective and economical measure to improve the iron status in developing countries that have a high rate of iron deficiency. Further studies are needed in order to clarify the relationship between the iron status and physical activity.

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J Phys Fitness Sports Med, **1(1)**: 167-174 (2012)

**JPFSM:** ***Regular Article***

# Regular exercise history as a predictor of exercise in community-dwelling older Japanese people

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Received: November 1, 2011 / Accepted: February 6, 2012

***Abstract*** A physically active lifestyle is important across the entire life span. However, little is known about life-long participation in regular exercise among older people. The purpose of the present study was to describe regular exercise throughout a person's lifetime and evaluate the impact of exercise earlier in life on participation in exercise at age 60 and over. The participants were 984 community-dwelling older people aged 60 to 86 years. Each participant's life was divided into five age categories: 12-19, 20-29, 30-39, 40-59, and 60 years and over. The association between exercise at an earlier age and that at 60 years and over was assessed using logistic regression analysis adjusted for potential confounders. Men had exercised throughout their lives more than women. Among women, participation in exercise during their 20s and 30s showed a sharp decline. The preference for exercise differed according to age and gender. Among men, the most common patterns of exercise throughout life were exercise during all the age categories, and starting exercise at age 60 and over; whereas in women the most common pattern was no exercise at all. The adjusted odds ratio of exercise at 40-59 years for exercise at age 60 and over was 5.85 (95% confidence interval: 3.82-8.96) among men and 6.89 (4.23-11.23) among women. Regular exercise in the younger age categories affected exercise at age 60 and over among men, but not among women. Regular exercise at 40-59 years was a strong predictor of exercise at 60 years and over in both men and women.

***Keywords*** : regular exercise, older people, life course, random sampling data

## Introduction

Physical activity is an important health behavior across the course of one's life. The benefits of physical activity in preventing health decline and physical function loss have been demonstrated, especially for frail and aged people[1)]. The Ministry of Education, Culture, Sports, Science and Technology in Japan reported that the participation rate of older people in physical activity and fitness has slightly increased in the past decade[2,3)]. However, more than 40 % of older people aged 70 years and older did not participate in any exercise during the past year[4)]. Insufficient physical activity remains a public health concern among older people in Japan.

Engaging in sports activities in childhood and adolescence is known to predict physical activity in adulthood[5)]. A low level of physical activity in early life has been found to predict physical inactivity in adulthood[6)]. However, most longitudinal studies have demonstrated that sports activities in early life have an effect on physical activity in young adulthood[5,6)]. It remains unclear whether sports activities in early life are associated with physical activity at an older age. Some studies have found that a history of physical activity was associated with current physical activity in older people[7,8)]. In an earlier study we found that the experience of exercise in adolescence was associated with a higher level of leisure-time physical activity in middle-aged and elderly Japanese women[9)]. However, little basic descriptive data exists on individual variation in participation in exercise throughout the life span and the impacts of early exercise on physical activity in later life among community-dwelling Japanese older people.

The purpose of the present study was to describe regular exercise throughout the life course and evaluate the effect of early exercise on the participation in exercise at the age of 60 years and over.

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## Methods

***Study population.*** The investigation is a part of the 4th survey of the National Institute for Longevity Sciences - Longitudinal Study of Aging (NILS-LSA), which is a follow-up study on the causes of geriatric diseases and health problems in older people. The NILS-LSA was based on data obtained from interviews and laboratory examinations of medical, nutritional, psychological, and physical fitness variables. The details of the study can be found elsewhere[10]. The initial survey of the NILS-LSA involved 2,267 men and women aged 40-79 years, including almost 300 men and 300 women for each decade (40s, 50s, 60s and 70s). The participants were gender- and decade age-stratified random samples of the residents of Obu-shi and Higashiura-cho, Aichi Prefecture, in central Japan. The participants were drawn from resident registrations in cooperation with local governments. All subjects lived or had lived at home in the community. The participants in the present study comprised 523 men and 461 women aged 60-86 years. All the NILS-LSA procedures were already approved by the Ethical Committee of the National Center for Geriatrics and Gerontology, and all of the participants signed a written informed consent.

***Measures and Procedures.*** Regular exercise was assessed using a questionnaire and an interview. The questionnaire was based on a questionnaire developed by the Japanese Lifestyle Monitoring Group[11]. The participants were asked for the type, time, frequency and duration of their regular exercise from the age of 12 years to the present with the question "What physical activities or sports have you participated in during these age categories?" The participants reported the types of physical activities and sports they had engaged in from a list of alternatives. These were coded as 1) light activities such as walking, gymnastic exercise and gardening, 2) moderate activities such as brisk walking, dancing and swimming for pleasure, 3) vigorous activities with increased breathing and sweating such as jogging and playing tennis, 4) exhausting activities such as various competitive sports. Frequency of participation was defined as how often they participated in physical activities or sports per week. The duration of each activity was calculated with 1 year as the basic unit. Physical activities or sports that were engaged in for at least 20 minutes, once a week and over 1 year, excluding physical education at school, were defined as regular exercise. Life span was divided into five age categories: 12-19, 20-29, 30-39, 40-59 and 60 years and over. The age categories of 40 and over included more years with reference to previous studies[7,8], showing physical activity to be stable in middle age[12].

If participants engaged in a number of regular exercises during the same period, the exercise with the longer duration was selected. Interviews were performed by trained staff.

Potential confounders, included age, education, marital status (never married, married, separated, divorced and bereaved), annual income (6,500,000 yen or less vs. more than 6,500,000 yen) and chronic conditions including smoking status (never, former and current), self-rated health (excellent, very good, good, fair and poor) and prevalent diseases (hypertension, ischemic heart disease, diabetes, osteoporosis, arthritis and cancer), were investigated using a questionnaire and interview by a physician. Height and weight were measured using a digital scale. Body mass index was calculated by weight divided by height squared (BMI; $kg/m^2$). Body fat mass was assessed by dual X-ray absorptiometry (DXA; QDR-4500A, Hologic, USA). Work-related physical activity was estimated using the same questionnaire developed by the Japanese Lifestyle Monitoring Group[11]. Work activities were assigned an intensity coefficient of 1.5, 2.5, 4.5 and 7.5 METs (metabolic equivalents) for sedentary work, work done standing or walking, moderately strenuous work and strenuous work, respectively. The work activity scores were calculated by multiplying the intensity coefficients by the total number of minutes spent on the activity over the last 12 months.

***Statistical analysis.*** The statistical significance of the differences in social and health conditions were analyzed by the Cochran-Mantel-Haenszel test for categorical variables and Student's t-test for continuous variables according to participation in regular exercise at age 60 and over. The participation rate in regular exercise was calculated as the percentage of participants who engaged in exercise in each age category. Gender differences in the participation rate in each age category were analyzed using Pearson's chi-squared test. The relationship between regular exercise in the younger age categories and at age 60 and over was evaluated using multiple logistic regression analysis. Both the unadjusted model and the model adjusted for all potential confounders were analyzed. The analyses were performed for men and women separately, as the gender difference in the participation rate in regular exercise was considerable. Statistical testing was performed using the Statistical Analysis System (SAS), release 9.1.3 (SAS Institute Inc. NC, USA). Probability levels of less than 0.05 were considered to be significant.

## Results

Table 1 shows the characteristics of the participants by gender according to participation in regular exercise at age 60 and over. The mean age of the study population was 70.0±6.6 years in men and 69.8±6.7 years in women. Age, weight, BMI, annual income, work-related physical activity, smoking, self-rated health, hypertension and arthritis for men; and height, education, work-related physical activity for women were associated with regular exercise at age 60 and over ($p<0.05$).

The participation rates in regular exercise for age categories 12-19, 20-29, 30-39, 40-59 and 60 years and over

**Table 1.** Charactaristics of the participants according to regular exercise at age 60 and over for men and women

| | | Men | | | Women | | |
|---|---|---|---|---|---|---|---|
| | | Regular exercise | | | Regular exercise | | |
| | | Yes | No | | Yes | No | |
| | | n=342 | n=181 | *p* -value | n=263 | n=193 | *p* -value |
| Age | years | **70.4 ± 6.3** | **69.2 ± 7.2** | **0.048** | 69.7 ± 6.4 | 70.2 ± 7.0 | 0.503 |
| Height | cm | 163.6 ± 5.7 | 162.7 ± 5.9 | 0.108 | **150.5 ± 5.6** | **149.1 ± 6.2** | **0.010** |
| Weight | kg | **62.3 ± 9.0** | **59.2 ± 8.3** | **<0.001** | 51.8 ± 7.7 | 51.7 ± 8.7 | 0.829 |
| BMI | $kg/m^2$ | **23.3 ± 2.8** | **22.3 ± 2.8** | **<0.001** | 22.9 ± 3.0 | 23.2 ± 3.4 | 0.246 |
| Body fat | % | 22.9 ± 4.4 | 22.5 ± 4.6 | 0.395 | 32.4 ± 5.1 | 32.6 ± 5.5 | 0.688 |
| Education | years | 11.9 ± 2.9 | 11.7 ± 3.0 | 0.513 | **11.1 ± 2.3** | **10.6 ± 2.5** | **0.033** |
| Marital status | % | | | 0.097 | | | 0.295 |
| Never | | 0.0 | 2.2 | | 3.1 | 3.7 | |
| Married | | 94.4 | 91.2 | | 71.7 | 64.0 | |
| Separation | | 0.6 | 0.6 | | 0.4 | 0.0 | |
| Divorce | | 0.6 | 0.6 | | 1.9 | 4.2 | |
| Bereavement | | 4.5 | 5.5 | | 23.0 | 28.0 | |
| Annual income | % | | | | | | |
| 6,500,000 yen and higher | | **24.8** | **35.2** | **0.013** | 25.8 | 29.4 | 0.401 |
| Work-related physical activity | METs*min* $10^{-3}$ | **130.8 ± 135.9** | **170.7 ± 151.7** | **0.002** | **183.0 ± 85.5** | **206.8 ± 109.0** | **0.010** |
| Smoking | % | | | **<0.001** | | | 0.910 |
| Never | | **24.8** | **20.3** | | 93.9 | 94.2 | |
| Former | | **58.1** | **47.3** | | 2.3 | 2.6 | |
| Current | | **17.1** | **32.4** | | 3.8 | 3.1 | |
| Self-rated health | % | | | **0.001** | | | 0.287 |
| Excellent | | **6.5** | **0.6** | | 3.8 | 5.2 | |
| Very good | | **33.3** | **24.7** | | 21.7 | 15.6 | |
| Good | | **52.2** | **63.2** | | 65.0 | 66.2 | |
| Fair | | **7.7** | **9.9** | | 9.1 | 12.5 | |
| Poor | | **0.3** | **0.6** | | 0.4 | 0.5 | |
| Prevalent diseases | % | | | | | | |
| Hypertension | | **44.5** | **31.3** | **0.003** | 40.7 | 41.2 | 0.921 |
| Ischemic heart diseases | | 6.2 | 9.3 | 0.188 | 7.2 | 6.8 | 0.852 |
| Diabetes | | 11.5 | 11.0 | 0.860 | 7.2 | 5.2 | 0.385 |
| Osteoporosis | | 1.2 | 3.3 | 0.093 | 16.4 | 17.2 | 0.827 |
| Arthritis | | **4.4** | **11.5** | **0.002** | 11.8 | 17.2 | 0.102 |
| Cancer | | 6.2 | 6.6 | 0.859 | 5.7 | 9.4 | 0.136 |

Continuous variables are presented as means ± standard deviation (SD), and categorical variables are presented as percentages. The differences between groups were analyzed by Student's t-test for continuous variables and by Cochran-Mantel-Haenszel test for categorical variables. Bold represents significant p-value (<0.05). BMI, Body mass index. METs, Metabolic equivalents

are shown Table 2. The percentage of men who had regular exercise was significantly higher than that of women in all of the age categories ($p<0.05$), except for 40-59 years. Among women, a large drop in the percentage reporting participation in exercise was found during the ages of 20-29 and 30-39 years.

The popular type of exercise reported for the different age categories is presented in Tables 3a and 3b. The most popular activities and sports differed both by gender and by age category. Men frequently reported team sports such as baseball and softball up to 40-59 years of age. In women, volleyball was frequently reported up to 30-39 years of age, while dancing and gymnastics exercise were more likely to be reported among those over 20 years of age. At age 60 and over, walking was the most popular exercise among both men and women.

All the possible patterns of participation in regular exercise from age 12 to the present were examined. Thirty-two

different patterns were identified (Figure 1). In men, the most common patterns were participation in regular exercise during all the age categories (12.6%) and participation in regular exercise at age 60 and over (12.6%). In women, the most common pattern was no regular exercise in any age category (21.1%), followed by participation in regular exercise at age 40 and over (14.3%).

Table 4 shows that participating in regular exercise at age 60 and over is related to participation in regular exercise across one's life span. The participants who had exercised at younger age categories were more likely to participate in exercise at age 60 and over for both men and women.

The odds ratios (OR) and 95% confidence intervals (CI) for those who regularly exercised at age 60 and over are shown in Table 5. Although, among men, the results of the unadjusted model for the age category 12-19 years was of borderline statistical significance (OR1.42, 95% CI 0.99-2.05), the odds ratio for participating in exercise at age 60 and over was higher for men who had regular exercise during each age category. The highest odds ratio was 4.63 (95%CI 3.07-6.98) among men who had regular exercise at 40-59 years. In women, regular exercise in the earlier age categories did not correlate with exercise at age 60 and over. However, the odds ratio for participating in exercise at age 60 and over was about six times higher among those who had regular exercise at 40-59 years (OR 5.85, 95%CI 3.82-8.96). After adjusting for age (continuous variable), BMI (continuous variable), education (continuous variable), annual income (6,500,000 yen or less/ more than 6,500,000 yen), work-related physical activity (1SD), smoking (never/ former/ current), self-rated health (excellent/ very good/ good/ fair/ poor) and chronic diseases (Yes/ No), the associations remained in both men and women. Regular exercise at 40-59 years was strongly associated with exercise at age 60 and over in both men (OR 5.96, 95%CI 3.72-9.57) and women (OR 6.89, 95%CI 4.23-11.23).

**Table 2.** Participation rate in regular exercise across the life course

| age (years) | Men (n=523) | | Women (n=461) | | *p* - value |
|---|---|---|---|---|---|
| | n | % | n | % | |
| 12-19 | 311 | 59.5 | 198 | 43.0 | <0.001 |
| 20-29 | 173 | 33.1 | 29 | 6.3 | <0.001 |
| 30-39 | 155 | 29.8 | 62 | 13.5 | <0.001 |
| 40-59 | 233 | 44.6 | 203 | 44.0 | 0.871 |
| 60 and over | 342 | 65.4 | 263 | 57.1 | <0.001 |

Numbers and percentages are shown for those who participated in regular exercise divided into five age categories. Pearson's chi-squared test. df=1.

## Discussion

The present study described regular exercise throughout a person's life and evaluated the impact of early regular exercise on participation in exercise at age 60 and over.

Previous longitudinal studies suggest that physical activity in early life tracks to later life[5,6]. However, most studies have tracked physical activity from childhood and adolescence to young adulthood and the coefficients re-

**Table 3a.** Popular types of regular exercise across the life course among men (n=523)

| age (years) | 1st | % | 2nd | % | 3rd | % |
|---|---|---|---|---|---|---|
| 12-19 | Baseball | 16.6 | Track & Field | 11.9 | Judo | 8.4 |
| 20-29 | Baseball | 11.9 | Softball | 4.6 | Table tennis | 4.0 |
| 30-39 | Golf | 7.6 | Softball | 6.5 | Baseball | 5.9 |
| 40-59 | | Golf / Walking * | 16.1 | | Softball | 7.6 |
| 60 and over | Walking | 34.4 | Brisk walking | 18.4 | Golf | 13.2 |

Percentages are shown for those who participated in the exercise. *, Both golf and walking share in 1st place with the same percentage.

**Table 3b.** Popular types of regular exercise across the life course among women (n=461)

| age (years) | 1st | % | 2nd | % | 3rd | % |
|---|---|---|---|---|---|---|
| 12-19 | Volleyball | 15.8 | Softball | 7.8 | Table tennis | 6.1 |
| 20-29 | Volleyball | 1.7 | Dancing | 1.3 | Tennis | 0.9 |
| 30-39 | Volleyball | 3.5 | Walking | 2.8 | Tennis, Dancing or Softball | 1.5 |
| 40-59 | Walking | 13.9 | Gymnastics exercise | 8.7 | Dancing | 8.5 |
| 60 and over | Walking | 24.7 | Gymnastics exercise | 15.4 | Brisk walking | 9.5 |

Percentages are shown for those who participated in the exercise.

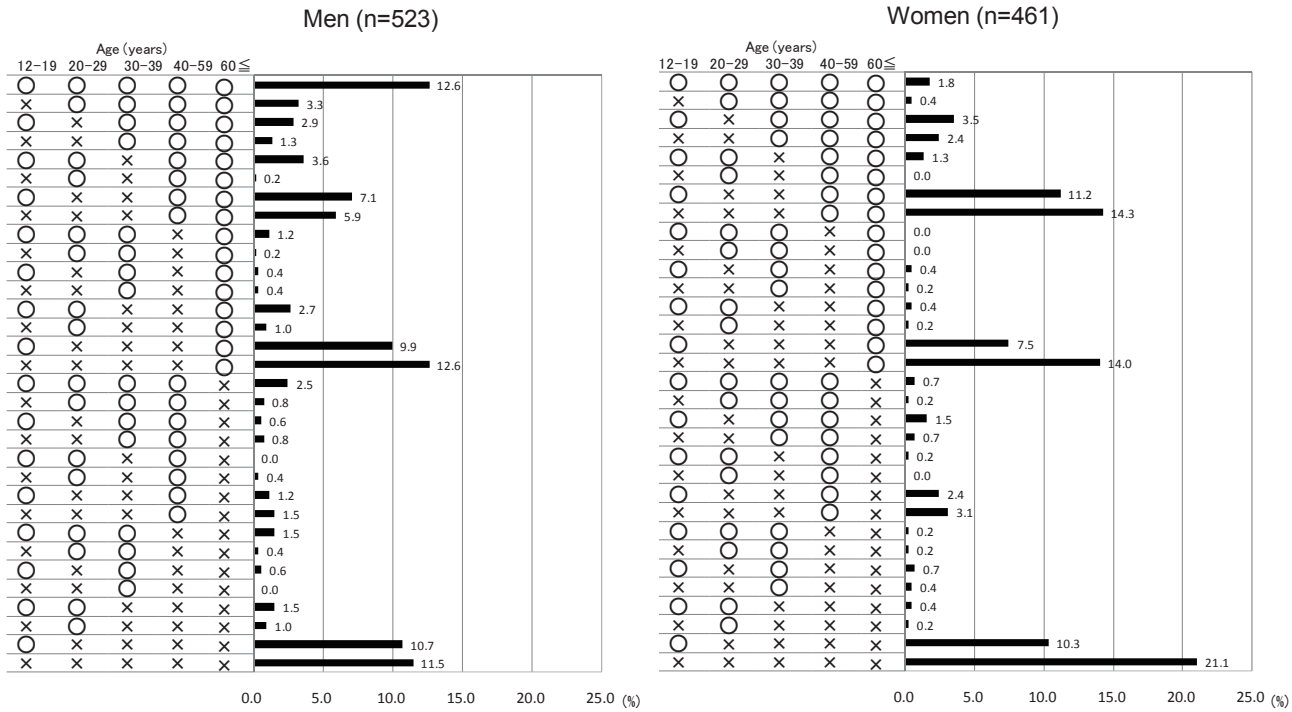


**Fig. 1** Participation pattern in regular exercise across the life course for men and women, separately
Regular exercise status: (○) = participants who engaged in regular exercise, (×) = participants who did not engage in regular exercise

**Table 4.** Distribution of participation in regular exercisre at age 60 and over according to participation in regular exercise across the life course

| age (years) | Regular exercise | Men (n=342) | | Women (n=263) | |
|---|---|---|---|---|---|
| | | n | % | n | % |
| 12-19 | No | 130 | 61.3 | 144 | 54.8 |
| | Yes | 212 | 62.0 | 119 | 60.1 |
| 20-29 | No | 213 | 60.9 | 244 | 56.5 |
| | Yes | 129 | 74.6 | 19 | 65.5 |
| 30-39 | No | 225 | 61.4 | 223 | 56.0 |
| | Yes | 117 | 75.5 | 40 | 64.5 |
| 40-59 | No | 148 | 51.3 | 104 | 40.3 |
| | Yes | 194 | 83.3 | 159 | 78.3 |

Numbers and percentage are shown for those who engaged in regular exercise at age 60 and over.

ported have been only low or moderate[5]. In another study, the correlation between the time points studied was found to weaken over time[13]. Only a few studies have examined whether physical activity in early life tracks to an older age. Retrospective findings that past physical activity predicts physical activity in older people[7,8] can help to explain the positive association between experiences of exercise and physical activity later in life. However, basic descriptive data on individual exercise history throughout life is lacking for the community-dwelling older people in Japan. Assessing life-long regular exercise and the contribution of past exercise experience to engagement in regular exercise later in life are the underlying considerations when promoting an active lifestyle throughout a person's life.

Our finding that men are more physically active than women throughout their lives is partially supported by pre-

**Table 5.** Odds ratio and 95% confidence interval for those who had regular exercise at age 60 and over

| | Model 1 | | | | Model 2 | | | |
|---|---|---|---|---|---|---|---|---|
| | Men | | Women | | Men | | Women | |
| | OR | 95%CI | OR | 95%CI | OR | 95%CI | OR | 95%CI |
| Regular exercise | | | | | | | | |
| At 12-19 years of age | 1.42 | 0.99 - 2.05 | 1.30 | 0.89 - 1.90 | **1.69** | **1.10 - 2.58** | 1.06 | 0.71 - 1.60 |
| At 20-29 years of age | **2.03** | **1.35 - 3.05** | 1.43 | 0.65 - 3.14 | **1.87** | **1.21 - 2.90** | 1.26 | 0.55 - 2.87 |
| At 30-39 years of age | **2.02** | **1.32 - 3.09** | 1.47 | 0.84 - 2.58 | **2.00** | **1.27 - 3.15** | 1.29 | 0.69 - 2.41 |
| At 40-59 years of age | **4.63** | **3.07 - 6.98** | **5.85** | **3.82 - 8.96** | **5.96** | **3.72 - 9.57** | **6.89** | **4.23 - 11.23** |

OR, odds ratio; CI, confidence interval. Model1: unadjusted, Model2: adjusted for age, BMI, education, income, work-related physical activity, smoking, self-rated health, chronic diseases. Bold represents significant p-value (<0.05)

vious studies[14,15]. Women may perceive more traditional, social and environmental barriers than men to engaging in exercise[8,15]. For instance, exercise has been considered "not ladylike"[16]. These aspects may in part be responsible for the lower rate of participation in exercise throughout life among women. Furthermore, a large drop in participation in exercise was observed among women in their 20s and 30s. The transition from adolescence to adulthood is a period of general decline in physical activity[17]. Some life changes, such as getting married and having children, affect physical activity in young adulthood in women more than in men[5]. National data in Japan show that the age of first marriage for men was 26.9 years and for women 24.2 years in 1970[18]. The most common age range for giving birth is 20-39 years[19]. After the fourth decade of life, most people's family and job situations seem to be established and stable. Retirement, in turn, tends to increase physical activity[20]. These life events may be associated with regular exercise. Further research on the relationship between life events and exercise is needed to clarify this issue.

The most popular activities and sports changed between the earlier and later age categories; there was also a gender difference in popular types of activities throughout life. Previous studies have reported a high frequency of ball games among men across ages 14 to 31 years[21]. Dance and gymnastics were more popular with women[15,22]. Our finding supports the previous gender difference in the traditional preferences for specific types of exercise. From the perspective of age, team sport activities were common in adolescence and young adulthood, and individual sports in middle age and older. A possible explanation of the shift is that social situations and lifestyle change according to age, for instance, it is more difficult for a large number of adults to get together, whereas individual sports can be performed in one's own time[21]. Individual sports are sometimes labeled lifetime sports[23] and adult-like activities[17]. Previous studies have reported walking and gardening as the most common activities among older adults[24]. To maintain their exercise levels, people may have to choose specific types of exercise as their lifestyles change with aging[25]. We may consider that older people who engage in regular exercise in our study are those who are able to find suitable activities to match their life changes.

In this study, we tracked regular exercise from adolescence to age 60 and over, and described the individual variation in participation in exercise. A number of participants reported participating in regular exercise at some time in their life, although reports of consistent engagement in regular exercise across several decades were scarce. We have already shown cross-sectionally in Table 2 that the prevalence of regular exercise in the 20s and 30s was low. Figure 1 illustrates the findings as individual transitions of regular exercise throughout life. Although the percentage in each pattern was small, and the patterns of exercise frequency seemed to be similar in both men and women, we found that among men the most frequent pattern was participation in regular exercise at all the life stages; whereas among women the most frequent pattern was no regular exercise at all. Results suggest that encouragement and support for older women should be provided by health professionals as well as the community, since participation in exercise may induce a major behavioral change among older women. There may be a need to tailor health promotion messages and interventions according to gender and personal exercise history.

After fully adjusting for confounding factors such as age, BMI, education, annual income, smoking, work-related physical activity, self-rated health, and chronic diseases, both men and women who had participated in regular exercise during 40-59 years of age had a 5 to 7-fold higher rate of participation in exercise at age 60 and over. This result suggests that participation in exercise during 40-59 years of age predicts exercise at age 60 and over. Our findings are in line with those of some previous studies[7,8]. Frändin et al. , who studied age groups from the age of 10 years, found that physical activity during earlier life was not correlated with physical activity at the age of 76, except for the last age period 66-76 years[7]. Other studies also found the last age group to be better predictors than earlier ones[8,26]. The short interval may be one of the causes for the strong relationship between regular exercise at 40-59 years of age and that at age 60 and over. A number of studies have suggested that childhood is usually considered the best time for socialization into physical activity[8], for encouraging physical activity in adults through the developing of habits[25] and for promoting exercise-related feelings of pleasure and joy[7]. Furthermore, sports activities may have an effect on motor and coordination skills that may be of value later in life[21]. We believe that the positive effects of exercise in early life are associated with physical activity in older life. In fact, regular exercise during all the age categories studied affected exercise at age 60 and over among men. However, demographic, psychological, behavioral, social and environmental factors are associated with adulthood participation in physical activity[27]. These multiple factors may decrease the positive effect of earlier exercise at older ages. Health problems were reported to be the most common barrier to increasing physical activity[28]. We found that the effect of regular exercise at 40-59 years of age on participation in exercise at age 60 and over increased among women who had a history of hypertension in the sub-analyses (data not shown). Chronic health problems may also have influenced the motivation for physical activity as a part of clinical care. Our finding that regular exercise during 40-59 years of age was associated with that at age 60 and over was true for a lot of people who had not engaged in regular exercise earlier in their lives. The motivation to engage in regular exercise in the fourth and fifth decades of life may have important implications for promoting increased physical activity in older age.

This study has several limitations. The first limitation

is that our study was a retrospective study and the regular exercise data were based on self-reports. Possible memory failure and potential recall bias may have influenced the results. In addition, we were not able to take into account the short-term substitution of one exercise for another as regular exercise was defined as an activity lasting one year. Therefore our study may underestimate regular exercise as an indicator of physical activity. Secondly, social and environment factors, which have been indicated as predictors of physical activity, were not widely examined in our study. Environmental factors are among the important factors promoting participation in physical activity[16]. Recent studies suggested that environmental problems, such as poorly lit streets or noisy traffic, are correlated with inactivity[29]. Further studies are needed to confirm the association between regular exercise and a comprehensive range of factors. Finally, the definition of regular exercise in this study was lower than the well-known recommendation of physical activity for adults by the American College of Sports Medicine[30]. However, we previously found that continuation of regular exercise by the same definition as used in this study was associated with higher muscle strength and power in both elderly men and women[31]. A number of older people are physically inactive. "Tojikomori", being housebound, which has been defined in recent studies as going outdoors once or less than once a week, is a serious concern in relation to older people[32]. Pate et al. suggest that an active lifestyle does not require a regimented, vigorous exercise program[33]. To avoid causing undue stress coming from misconceptions, it may be sufficient just emphasizing to older people the importance of being physically active as opposed to having to maintain a disciplined workout schedule.

The strengths of the present study include a large number of randomized community-dwelling people and regular exercise data tracked from age 12 to 60 years and over. These data provide important information for demonstrating the value of life-long physical activity. The participants had a face-to-face interview by trained staff, which increases the reliability of the answers and reduces missing data in the questions. We were able to take into account essential social and health condition data such as education, smoking and disease as confounders. Our study described individual variation in regular exercise throughout the various stages of a person's life and showed the positive impact of experiences of exercise in earlier life on regular exercise in later life; and thus lays a good foundation for persuading the general population of the importance of maintaining physical activity throughout life.

## Conclusion

The present study found that men engaged in regular exercise more than women throughout their lifetime. Exercise preferences differed depending on age and gender. Among women, those reporting no regular exercise were the largest group. Among men, regular exercise earlier in life positively affected regular exercise at age 60 years and over. Regular exercise in middle age markedly increased participation in exercise later in life regardless of social and health conditions among both men and women.

**Acknowledgments**

The authors would like to thank the participants and also colleagues in the NILS-LSA. This study was supported by a Grant-in-Aid for Young Scientists (A) from the Japan Society for the Promotion of Science (#20680034).

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