Hypoxia inducible factor 1-alpha in the pathogenesis of abdominal aortic aneurysms in vivo: A narrative review

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ABSTRACT

Abdominal aortic aneurysms (AAAs) are relatively common, primarily among older men, and, in the case of rupture, are associated with high mortality. Although procedure-related morbidity and mortality have improved with the advent of endovascular repair, noninvasive treatment and improved assessment of AAA rupture risk should still be sought. Several cellular pathways seem contributory to the histopathologic changes that drive AAA growth and rupture. Hypoxia inducible factor 1-alpha (HIF-1α) is an oxygen-sensitive protein that accumulates in the cytoplasm under hypoxic conditions and regulates a wide array of downstream effectors to hypoxia. Examining the potential role of HIF-1α in the pathogenesis of AAAs is alluring, because local hypoxia is known to be present in the AAA vessel wall. A systematic scoping review was performed to review the current evidence regarding the role of HIF-1α in AAA disease in vivo. After screening, 17 studies were included in the analysis. Experimental animal studies and human studies show increased HIF-1α activity in AAA tissue compared with healthy aorta and a correlation of HIF-1α activity with key histopathologic features of AAA disease. In vivo HIF-1α inhibition in animals protects against AAA development and growth. One study reveals a positive correlation between HIF-1α–activating genetic polymorphisms and the risk of AAA disease in humans. The main findings suggest a causal role of HIF-1α in the pathogenesis of AAAs in vivo. Further research into the HIF-1α pathway in AAA disease might reveal clinically applicable pharmacologic targets or biomarkers relevant in the treatment and monitoring of AAA disease. (JVS—Vascular Science 2024;5:100189.)

Keywords: AAA; Abdominal aortic aneurysm; HIF-1α; Hypoxia inducible factor 1-alpha

Abdominal aortic aneurysm (AAA) disease is a relatively common and potentially fatal disease of the abdominal aorta, primarily among older men.[1] The predominant risk factors for AAA development include age, male gender, tobacco smoking, hypertension, and a family history of AAA disease.[2] Aneurysm rupture is a highly fatal event, with a mortality rate approaching 80%.[3] Because no pharmacologic therapies have yet proved effective in limiting AAA growth and rupture risk, the current management is prophylactic repair of large and/or rapidly growing AAAs by either open or endovascular aneurysm repair.[4-6] Although procedure-related morbidity and mortality rates have improved with the advent of endovascular aneurysm repair, noninvasive treatment and improved assessment of AAA growth and rupture risk should still be sought.[5,6]

The AAA vessel wall is characterized by inflammation, oxidative stress, neovascularization, and proteolytic degradation.[7] Although not yet completely understood, a number of cellular pathways seem contributory to the histopathologic changes that drive AAA growth and rupture.[8-12] Hypoxia inducible factor 1-alpha (HIF-1α) is an oxygen-sensitive protein that accumulates in the cytoplasm under hypoxic conditions and, after translocation to the nucleus, heterodimerizes with HIF 1-beta to form the active transcription factor HIF-1. Hypoxia is a well-known regulator of HIF-1α at the protein level, mainly through stabilization rather than degradation; however, it can also affect gene expression, although this is not the main method of regulation. The effects on gene expression can be context dependent, varying with cell type and the specific cellular environment.

HIF-1 regulates a wide array of downstream effectors, including angiogenic, proliferative, and metabolic responses to hypoxic conditions[13] (Fig 1). Transcription of HIF-1α is increased in response to growth hormones, reactive oxygen species, and inflammatory cytokines.[14,15] Examining the potential role of HIF-1α in the

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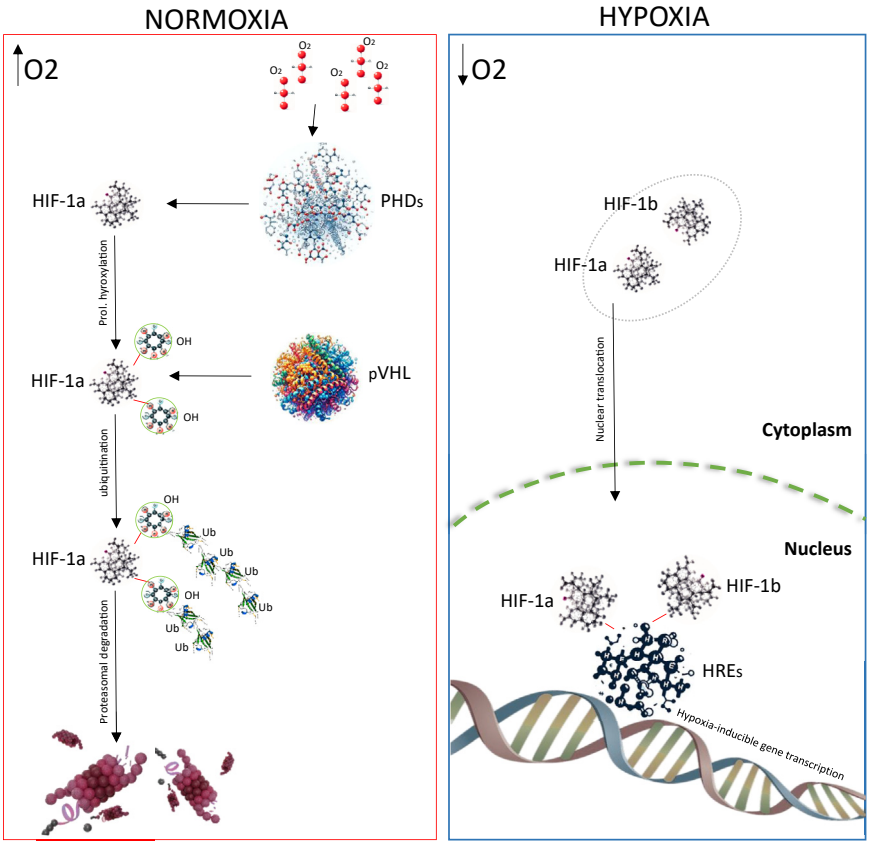

Fig 1. Regulation of hypoxia-inducible factor 1α (HIF-1α) at different levels and conditions. Under normal oxygen (O_2) tension (normoxia), HIF-1α protein is hydroxylated at two proline residues by a group of enzymes called prolyl-4-hydroxylases (*PHDs*). It then associates with von Hippel-Lindau protein (*pVHL*) and is tagged with ubiquitin, resulting in proteasomal degradation. HIF-1, when stabilized by hypoxic conditions, is translocated to the cell nucleus and associates with HIF-1 beta (*HIF-1b*). This complex binds to hypoxia-responsive elements (*HREs*) in promoters, resulting in gene transcription.

pathogenesis of AAA is alluring, and this study aimed to review the current evidence regarding the role of HIF-1α in AAA disease in vivo.

METHODS

We drafted and revised a protocol using the PRISMA-P (preferred reporting items for systematic reviews and meta-analysis protocols). The final protocol was registered prospectively with the Open Science Framework on May 5, 2021 (available at: osf.io/v96x5; DOI: 10.17605/OSF.IO/2QSKU).

Eligibility. Experimental animal AAA induction studies with HIF-1α-assays and/or HIF-1α inhibition or knockout or silencing and studies of human participants with AAAs and HIF-1α assays reported in peer-reviewed biomedical journals were included. Narrative reviews, systematic reviews, and conference abstracts were excluded. Studies including thoracoabdominal aortic aneurysms were excluded. Animal studies with AAA induction by deliberate hypoxia were excluded. There were no restrictions on the number of patients or test subjects. The language was restricted to English, German, Danish, Swedish, or Norwegian.

Search strategy. EMBASE and PubMed were searched to identify potentially relevant publications. The search strategy was drafted in collaboration with a librarian from the Copenhagen University Library and was further refined through team discussion. The final search strategy for PubMed is presented in Fig 2. A similar search was conducted in EMBASE, and the final search was conducted on June 22, 2023. The results were exported to Covidence (available at: www.covidence.org), and duplicates were removed by team revision.

Screening process. The screening process was conducted independently by two physicians using Covidence. First, the titles and abstracts were screened according to the eligibility criteria, and discrepancies were discussed until a consensus was reached by all of us. The same procedure was conducted for the full-text screening.

Data extraction and primary and secondary outcomes. Data extraction was only conducted by one physician. A data extraction checklist was developed to extract data relevant to describe the primary and secondary outcomes. The primary outcome was to describe

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Fig 2. PubMed search strategy.

the role of HIF-1α in the pathogenesis of AAA. The secondary outcome was to describe the correlated effects to HIF-1α activity in AAA patients and animal models, including leukocyte infiltration, elastin degradation, collagen degradation, and matrix metalloproteinase activity. Data regarding the following variables were extracted to an Excel spreadsheet (Microsoft): study design; number of participants; AAA-induction method; case, control, and sham group characteristics; HIF-1α inhibition method; AAA occurrence rate; AAA severity score; aortic diameter; AAA rupture rate; HIF-1α gene expression; HIF-1α enzymatic activity; and mutations in genes linked to HIF-1α expression.

Synthesis of results. To synthesize our results, the data were narratively grouped, primarily by study type, population, and intervention, to account for the expected diverse methodologic nature of the included studies. Due to the scarcity of data, there was no sufficient basis for the statistical synthesis required for a meta-analysis.

RESULTS

AAA growth is connected to ischemia and inflammation of the AAA vessel wall. However, despite HIF-1α being elevated by reactive oxygen species and inflammation, studies examining associations between HIF-1α and AAA are sparse. In this narrative review, 17 relatively inhomogeneous studies examining the correlations between AAA and HIF-1α were identified. Of these 17 studies, 6 presented exclusively experimental animal data, 8 presented exclusively human data, and 3 presented both animal and human data. The screening process is summarized in Fig 3, and the included studies are listed in the Table, with an overview of the study populations, methods, and interventions.

HIF-1α gene expression and concentration in experimental animal AAA models. The results from the included animal studies with a total of 361 animals show that experimentally induced AAAs are characterized by significantly increased HIF-1α gene expression and HIF-1α protein concentration in aneurysmatic tissue compared with healthy controls.[16,17,21,22,25,30,31]

In vivo inhibition of HIF-1α in experimental animal AAA models. Various methods of in vivo HIF-1α inhibition were applied in the included studies. Two studies by Wang et al[16,21] and one by Tsai et al[25] showed that pharmacologic inhibition with 2-methoxyestradiol and digoxin significantly decreased the AAA formation rate, AAA growth, and the AAA rupture rate and attenuated local HIF-1α expression, matrix metalloproteinase (MMP) activity, vascular endothelial growth factor (VEGF) expression, and

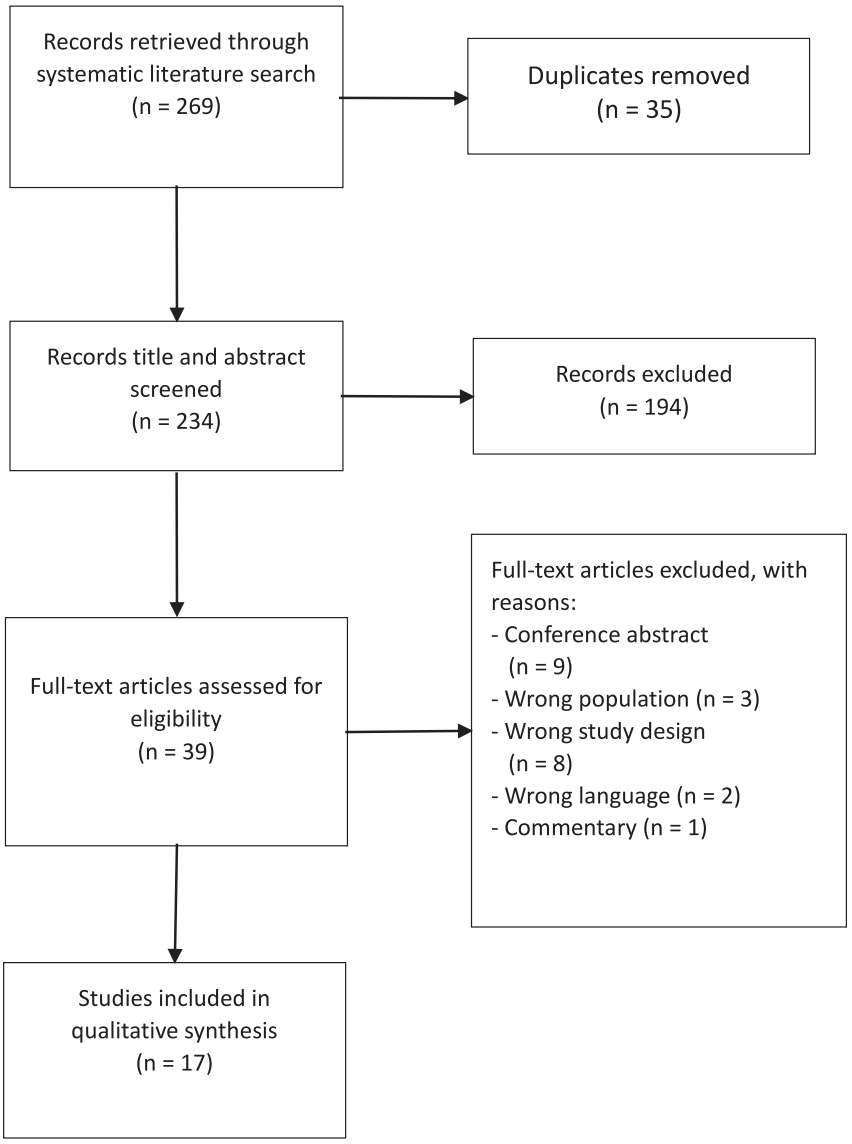

Fig 3. Overview of the screening process.

elastin breakdown. Pharmacologic HIF-1α inhibition with celecoxib and quercetin was shown in one study of 80 mice to attenuate AAA growth, HIF-1α expression, and protein concentration and to prevent medial neovascularization.[16] In vivo HIF-1α knockout with shRNA in an AAA-induction model with 60 mice showed that HIF-1α–inhibited mouse aortas had significantly smaller vessel diameters compared with controls and that HIF-1α inhibition prevented medial and elastin breakdown, leukocyte infiltration, and MMP activity.[24] Li et al[31] showed that in vivo silencing of H19, a long noncoding RNA with HIF-1α as its main downstream effector, inhibited AAA growth, decreased HIF-1α expression, and attenuated vascular smooth muscle cell (VSMC) apoptosis.

HIF-1α gene knockout in murine AAA models. Two studies of genetic HIF-1α knockout in murine experimental AAA models were included. The studies included a total of 89 mice. One study showed that genetic knockout of myeloid-specific HIF-1α significantly increased the aortic diameter in an AAA model compared with controls but did not find significant increases in the AAA formation rate, rupture rate, or AAA severity score.[17] A study by Imanishi et al[22] showed that genetic knockout of smooth muscle cell-specific HIF-1α did not affect the aortic diameter or AAA formation rate compared with controls, although knockout did significantly increase elastin breakdown and VSMC apoptosis.

HIF-1α expression and concentration in human AAA disease. The results from histopathologic analyses across the included studies of a total of 301 humans show that HIF-1α expression and concentration is increased in human AAA tissue compared with healthy aortic tissue.[18,21,26-29,31,32]

Table. General characteristics of included studies

Investigator	Population	Method	Case group, n	Control group, n	Sham group, n
Wang et al[16]	Animal model (mice)	AAA induction by periaortic application of $CaCl_2$; HIF-1α inhibition with quercetin and celecoxib	Quercetin, 20; celecoxib, 20	20	20
Takahara et al[17]	Animal model (mice)	AAA induction by high fat diet and angiotensin-II infusion; HIF-1α knockout by genetic deletion	18	11	NA
Blassova et al[18]	Human	Histologic study of human AAA sacs vs nonaneurysmatic aortic wall	39	8	NA
Gäbel et al[19]	Human	Gene expression comparison between patients with ruptured and nonruptured AAAs	17	31	NA
Choke et al[20]	Human	Histologic study of AAA rupture edge vs nonruptured AAA sac	12	12	NA
Wang et al[21]	Human and animal model (mice)	Gene expression comparison between human AAA patients healthy controls; AAA induction in mice by porcine pancreatic elastase infusion; HIF-1α inhibition by 2-ME or digoxin	Human, 24; mice, varied between assays	Human, 6; mice, varied between assays	NA
Imanishi et al[22]	Animal model (mice)	AAA induction by β-aminopropionitrile and angiotensin-II infusion; inhibition of smooth muscle cell-derived HIF-1α by genetic knockout	31	29	NA
Strauss et al[23]	Human	Genomic analysis of AAA patients vs healthy controls	518	541	NA
Yang et al[24]	Animal model (mice)	AAA induction by angiotensin-II infusion in apolipoprotein E-deficient mice; HIF-1α inhibition by in vivo knockout with shRNA	20	20	20
Tsai et al[25]	Animal model (mice)	AAA induction by high fat diet and angiotensin-II infusion; HIF-1α inhibition by 2-ME or digoxin	20	2-ME, 20; digoxin, 20	NA

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Table. Continued.

Investigator	Population	Method	Case group, n	Control group, n	Sham group, n
Kelly et al[26]	Human and animal model (mice)	Histologic study of human AAA patients vs healthy controls; AAA induction in mice with $CaPO_4$ and angiotensin-II infusion	Human, 4; $CaPO_4$, 5; angiotensin-II, 4	Human, 3; mice, 3	NA
Erdozain et al[27]	Human	Histologic study of AAA patients vs healthy controls	36	12	NA
Sano et al[28]	Human	Histologic study of AAA patients vs healthy controls	20	20	NA
Tanaka et al[29]	Human	Histologic study of aneurysmatic vs nonaneurysmatic aortic regions of AAA patients	30	11	NA
Van Vickle-Chavez et al[30]	Animal model (mice)	AAA induction by elastase perfusion	61	68	NA
Li et al[31]	Human and animal model (mice and pigs)	Histologic study of AAA patients vs healthy controls; AAA induction in mice by angiotensin-II infusion in apolipoprotein E-deficient mice; AAA induction in pigs by porcine pancreatic elastase infusion; HIF-1α inhibition via in vivo knockout of H19	Human, 20; mice, 4; pigs, 6	Human = 10	Mice, 4; pigs, 6
Grossmannova et al[32]	Human	Histologic study of AAA patients vs healthy controls	15	49	NA

AAA, Abdominal aortic aneurysm; *HIF-1α*, hypoxia inducible factor 1-alpha; *2-ME*, 2-methoxyestradiol; *NA*, not applicable.

Three studies found a positive correlation between HIF-1α activity and inflammatory cell infiltration, and one study showed a negative correlation with collagen concentration.[18,19,29,32] One study identified HIF-1α activity in all AAA vascular layers and specifically found increased HIF-1α activity in vasa vasorum VSMCs in areas in which VSMC proliferation caused vasa vasorum stenoses.[29] Similarly, Li et al[31] found increased HIF-1α activity in areas with VSMC apoptosis. Increased HIF-1α activity was shown in four studies to correlate positively with MMP expression,[8,17,26,29] and Wang et al[16] found a positive correlation with VEGF expression. Grossmannova et al[32] found a positive correlation between HIF-1α activity and the presence of carbonic anhydrase IX activity in AAA tissue.

HIF-1α in terminal AAA disease in humans. Two studies with a focus on HIF-1α and AAA rupture in 72 humans were included.[19,20] Histopathologic comparison of the rupture edge of ruptured AAAs with the nonruptured area of the same AAA revealed that HIF-1α activity was significantly increased in the rupture edge.[20] Additionally, it was found that increased HIF-1α was not associated with increased lactate concentration or ADP/ATP ratio, indicating a local state of preserved aerobic metabolism and decreased protein expression. One study compared the gene expression profiles of tissue biopsies from ruptured AAAs with those of nonruptured AAAs and found that the expression of HIF-1α–related genes was significantly increased in ruptured AAA tissue.[19] None of the studies offer substantial information concerning the methods of tissue extraction or the duration before the tissue samples were frozen.

Genetic correlation between human AAA disease and HIF-1α–related genes. Strauss et al[23] conducted a genomics study of 518 AAA patients and 541 healthy controls and found that polymorphisms in HIF-1α–related genes, leading to increased HIF-1α protein expression

and capacity coupled with VEGF-related gene polymorphisms, was an independent risk factor for AAA development. Likewise, HIF-1α–related gene polymorphisms, coupled with existing peripheral arterial disease, was found to be an independent risk factor for AAA development.[23]

DISCUSSION

This narrative review was conducted to map the current evidence regarding the role of HIF-1α in the pathogenesis of AAAs in vivo. Seventeen studies that reported data concerning this question were identified. The included studies report, in a near consensual manner, a positive correlation between the HIF-1α pathway and AAA development.

The strongest data on the role of HIF-1α can be gathered from knockout mouse studies. The included animal studies show that HIF-1α activity is linked to AAA development and a wide array of key histopathologic changes known to drive AAA growth and rupture. These findings are substantiated by animal studies showing that in vivo inhibition of HIF-1α protects against AAA development and AAA rupture and attenuates detrimental histopathologic characteristics of AAA disease. However, two included studies found that genetic knockout of HIF-1α in two specific cell lines did not affect AAA development, indicating a complex role of HIF-1α in the pathogenesis of AAAs.

The effect of HIF-1α inhibition on human AAA disease has not been studied. However, the included human studies consensually confirm the findings from the animal studies that HIF-1α activity is increased in AAA tissue and that HIF-1α activity is linked to histopathologic characteristics of AAA disease. A genomics study found that polymorphisms leading to increased HIF-1α activity accentuated AAA development, further indicating a possible translational potential of HIF-1α inhibition in the treatment of AAA disease in humans.

The development of HIF-1α inhibitors has been an area of significant interest, especially in the field of oncology, where it has been shown to promote tumor growth and survival under hypoxic conditions.[33,34] HIF-1α inhibitors aim to disrupt the HIF-1α pathway, thus, potentially inhibiting the adaptation of cancer cells to hypoxia and impeding their survival and proliferation.[35,36]

Research and development in this field are ongoing, with some inhibitors in preclinical and clinical trials. The complexity of the HIF-1 pathway and its extensive role in physiologic processes, however, poses challenges in developing inhibitors that are both effective and safe. As such, detailed information on the pharmacodynamics, pharmacokinetics, and potential side effects of these inhibitors is critical for their advancement in clinical therapies.

Study limitations. The present study was designed as a narrative review, with this method's inherent limitations, to synthesize data between studies that, by their nature, could not be expected to be quantitatively comparable. The included studies are, in general, small and include assays of differing methods, rendering a direct quantitative comparison between studies impossible. Importantly, studies of HIF-1α inhibition carry an inherent risk of a collateral effect due to many HIF-1α inhibitors being nonspecific. Another limitation was the small number of eligible studies, underlining the sparse research on the relationship between HIF-1α activity and AAA disease in vivo. However, the findings of this review seem generalizable to the current evidence status in this niche field.

CONCLUSIONS

The current evidence suggests that HIF-1α is a contributory causal factor in the pathogenesis of AAAs in vivo. Although research in this specific field is still scarce, the near-consensual results of the included studies indicate that further research on the role of the HIF-1α pathway in human AAA disease is alluring. Further research into the HIF-1α pathway in AAA disease might reveal clinically applicable pharmacologic targets or specific biomarkers relevant to monitoring and treating human AAA disease.

AUTHOR CONTRIBUTIONS

Conception and design: PB, MJ
Analysis and interpretation: PB, MJ, JE, QG
Data collection: PB, MJ
Writing the article: PB, MJ, JE, QG
Critical revision of the article: PB, MJ, JE, QG
Final approval of the article: PB, MJ, JE, QG
Statistical analysis: Not applicable
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Overall responsibility: QG

DISCLOSURES

None.

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