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Cigarette exposure and aging pathways: interplay between IGF-1 suppression and TGF-β increase

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Abstract

Chronic cigarette smoke exposure accelerates biological aging through sustained oxidative stress, DNA damage, and low-grade inflammation, thereby perturbing tissue homeostasis—notably by suppressing insulin-like growth factor-1 (IGF-1) signaling and activating transforming growth factor-β (TGF-β) pathways. Given the inconclusive evidence linking smoking or cotinine with circulating IGF-1 and TGF-β, we examined the association between blood cotinine and these biomarkers among healthy volunteers in Yogyakarta. This research was a cross-sectional study involving 106 healthy males and females aged 18-65 years. The data on smoking habits were collected through interviews guided by a questionnaire. Hemogram and blood chemistry examinations were done using spectrophotometric methods, while the levels of cotinine, IGF-1, and TGF-β were measured using ELISA. An independent t-test was used to compare mean levels between smokers and non-smokers groups. Pearson correlation was used for bivariate analysis to determine the association between cotinine and IGF-1 and TGF-β levels. Compared with non-smokers, active smokers exhibited markedly higher blood cotinine (41.97 ± 20.54 *vs.* 9.70 ± 4.20 ng/mL; $P < 0.001$), lower IGF-1 (55.06 ± 27.39 *vs.* 78.84 ± 22.23 ng/mL; $P < 0.001$), and higher TGF-β1 (238.60 ± 89.02 *vs.* 167.48 ± 104.54 ng/mL; $P = 0.001$). Across participants, cotinine correlated negatively with IGF-1 ($r = -0.608$; $P < 0.001$) and positively with TGF-β1 ($r = 0.281$; $P = 0.004$). In conclusion, cigarette smoking and cotinine levels were associated with IGF-1 suppression and TGF-β elevation in healthy volunteers in Yogyakarta.

Keywords: Aging, smoking, cotinine, IGF-1 level, TGF-β level

Introduction

Aging is a progressive biological process marked by declining physiological function, accumulating cellular damage, and systems-level dysregulation that increases the risk of degenerative disease [1]. In Indonesia, demographic shifts are accelerating. Older adults (≥ 60 years) already comprise over 10% of the population (~29 million in 2023); the country ranks sixth in life expectancy among ASEAN members and is projected to become an "aging society" by 2030 [2, 3]. Converging public-health data implicate modifiable exposures—particularly cigarette smoking, malnutrition, physical inactivity, and air pollution—as key drivers of premature aging [4, 5]. Smoking remains exceptionally prevalent in Indonesia's productive age groups. Among adolescents (13–18 years), prevalence is 38.3%, far exceeding rates in Malaysia (20.6%), Thailand (17.2%), and Myanmar (17%), with a mean initiation age of ~16.8 years, the youngest in Southeast Asia [6]. Early-life exposure to nicotine and smoke toxicant carries lasting consequences, including impaired lung growth, disrupted organ development, and altered brain maturation, and substantially increases lifetime risk of chronic disease and accelerated aging [7]. Chronic cigarette smoke exposure is believed to accelerate biological aging even before clinical symptoms manifest [8, 9]. Although cigarettes contain toxic compounds such as nicotine, tar, and aldehydes with pro-oxidant and pro-inflammatory properties, the specific mechanisms by which smoking modulates IGF-1 and TGF-β1 in healthy individuals have not been

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systematically investigated in Indonesia [10]. As cohorts with early smoking initiation transition into adulthood and older age, primary care systems are already seeing earlier-than-expected presentations of degenerative conditions, intensifying the burden on services. These trends underscore an urgent need to delineate mechanistic links between smoking behavior, cotinine level, and premature aging in Indonesian populations. Quantifying circulating IGF-1 and TGF-β1 would provide complementary readouts of growth-factor signaling and profibrotic/inflammatory activation [11, 12]. Understanding these mechanisms may serve as a foundation for developing preventive and promotive health strategies and evidence-based education on the detrimental effects of smoking, particularly within primary healthcare settings.

IGF-1 is vital in promoting cell proliferation, protein synthesis, tissue regeneration, and protection against apoptosis. It activates the PI3K/Akt and mTOR pathways, which are essential for cell survival and function, particularly in the nervous system, skeletal muscle, and skin. Recent studies indicate that optimal IGF-1 levels are associated with improved neuroplasticity, increased muscle strength, higher bone density, enhanced cognitive function, and reduced oxidative stress and systemic inflammation [13, 14]. Conversely, low IGF-1 levels are linked to sarcopenia, osteoporosis, metabolic disorders, and diminished tissue resilience, which accelerate biological aging [15]. External factors, notably as cigarette smoke, are believed to suppress IGF-1 expression by increasing oxidative stress and activating inflammatory pathways [11, 16].

TGF-β1 is a pleiotropic cytokine that regulates inflammation, fibrosis, and immune suppression [17, 18]. While essential for wound healing and inflammation control, excessive TGF-β1 triggers fibrogenesis, cellular senescence, and structural tissue damage through Smad-dependent and non-Smad pathways, such as MAPK and ERK [19]. Recent studies have demonstrated that elevated TGF-β1 levels are strongly associated with pathological aging, including pulmonary fibrosis, vascular stiffness, neurodegeneration, and stem cell decline [20]. Cigarette smoke is a significant activator of TGF-β1 signaling by increasing ROS production and causing mitochondrial dysfunction, thereby accelerating tissue damage [12]. However, in Indonesia, only few studies have directly explored the relationship between smoking and biological aging through molecular biomarkers such as IGF-1 and TGF-β1. Therefore, this research aims to fill this knowledge gap, provide scientific evidence on the molecular mechanisms of smoking-induced aging, and strengthen tobacco control and premature-aging prevention strategies in primary care. Molecular biology approaches are required to elucidate these signaling interactions in the context of aging. This study evaluates the impact of cigarette smoke exposure on IGF-1 and TGF-β1 levels in healthy individuals in Yogyakarta to clarify the molecular pathways of smoking-induced aging.

Materials

Research design and variables

This study employed an analytical observational design with a cross-sectional approach. The research was conducted in Yogyakarta, Indonesia, and the study protocol was reviewed and approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta (ref No: KE/FK/847/EC).

The independent variables comprised demographic characteristics and smoking-related exposures, including self-reported smoking behaviors and blood cotinine concentrations. Active smoking was defined in accordance with the Global Adult Tobacco Survey (GATS) as current smoking of any smoked tobacco product, either daily or less than daily. In addition, use of other tobacco products (*e.g.*, chewing tobacco) within the past five years was classified as smokeless tobacco use. Passive smoking (exposure to second-hand tobacco smoke) was defined as non-smokers exposed to smoke from burning tobacco products and/or smoke exhaled by smokers in homes, workplaces, or public places. Non-smokers were defined as individuals who did not currently smoke and either had never smoked or had smoked fewer than 100 cigarettes in their lifetime. Smoking behavior was assessed through interviewer-administered questionnaires and corroborated by measurement of blood cotinine using an ELISA kit [21].

In this study, the dependent variables captured complementary facets of aging biology in the context of tobacco exposure: circulating insulin-like growth factor-1 (IGF-1), its principal binding protein IGFBP-3, and transforming growth factor-β (TGF-β). IGF-1 reflects anabolic and reparative capacity and typically declines with age, while IGFBP-3 modulates IGF-1 bioavailability and thus influences signaling of the IGF axis. In contrast, TGF-β is a central mediator of profibrotic remodeling, cellular senescence, and low-grade inflammation. Together, these markers provide a biologically coherent readout of the hypothesized pathway by which smoking accelerates aging—namely, suppression of IGF-1 signaling coupled with upregulation of TGF-β–driven inflammatory and fibrotic responses [22, 23].

Subjects

The inclusion criteria were Indonesian (Javanese, Sundanese, Malay) ethnicity; healthy individuals between 18 and 65 years with no self-reported non-communicable diseases; and willingness to participate in the study by signing informed consent and cooperating throughout the study. We excluded subjects with congenital kidney disease, history of kidney transplantation, mental illness, or growth disorders (dwarfism/gigantism).

We calculated the sample size based on an expected Pearson correlation coefficient of 0.3 to 0.5. The primary independent variable was cigarette smoke exposure, assessed through serum cotinine levels, while the dependent variables were serum levels of IGF-1 and TGF-β1. To determine the required sample size, we used Pearson's correlation test with a significance level (α) of 5% and statistical power (1–β) of 80%. The sample size estimation followed Cohen's formula [24]:

Table 1. Smoking habit, demographic, and clinical characteristics of healthy volunteers in Yogyakarta Special Region, Indonesia.

No	Characteristics of participants		Freq (percentage)/mean(SD)
1	Gender	Men	70 (66.30%)
		Women	36 (33.70%)
2	Age group	45 years	40 (37.74%)
		46-60 years	50 (47.17%)
		> 60 years	16 (15.09%)
3	Regencies	Urban	33 (31.13%)
		Rural	73 (68.87%)
4	Education	≥ Elementary school graduates	48 (45.28%)
		junior and senior high school graduates	44 (41.51%)
		University	15 (14.15%)
5	Occupation	Civil servants, military, and police	12 (11.32%)
		Private and self-employed	64 (60.38%)
		Unemployed	30 (28.30%)
6	Marital status	Married	103 (97.17%)
		Not married	3 (2.83%)
7	Smoking habit	Smoking	31 (33.96%)
		Not smoking	75 (66.04%)
8	Cotinine (ng/mL)		19.14 ± 18.72
9	Random blood sugar (mg/dL)		107.20 ± 37.94
10	Triglyceride (mg/dL)		122.25 ± 70.30
11	Urea (mg/dL)		37.54 ± 38.02
12	IGF-1 (ng/mL)		71.88 ± 26.09
13	IGFBP-3 (ng/mL)		1584.44 ± 706.68
14	TGF-β (ng/mL)		188.28 ± 104.99
15	Treg (cells/μL)		25.02 ± 7.37

$n = [(Z\alpha + Z\beta)^2] / [0.5 \times \ln((1 + r)/(1 - r))]^2 + 3$

Where:

- $Z\alpha = 1.96$ (for $\alpha = 0.05$)
- $Z\beta = 0.84$ (for 80% power)
- r = expected correlation (between 0.3 and 0.5)

Based on these parameters, the minimum sample size required was 85 participants. Considering that approximately 33% of the population was smokers, this resulted in an estimated 28 smokers and 57 non-smokers.

Materials and instruments

This study used primary data collected through questionnaires and secondary data obtained from forms. The questionnaire collected demographic and smoking behavior data. The ELISA setup included two calibrated micropipettes measuring 10-100 mL and 100-1000 mL, a microspectrophotometer (Micro ELISA reader), a 1 mL measuring pipette, a 2.5 mL syringe for venous blood collection, a venoject for plasma storage, serum, and gloves. Cotinine, IGF-1, IGFBP-3, and TGF-β levels were measured with an ELISA kit at the Clinical Pathology Laboratory, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada (UGM).

Research procedures

Subject recruitmen

Subjects were selected based on the predefined inclusion and exclusion criteria. We recruited 106 healthy volunteers from five regencies in Daerah Istimewa Yogyakarta province. Potential subjects who met the inclusion criteria received an explanation of the study purpose. They signed informed consent to indicate their agreement to participate.

Data Collection

Socio-demographic and lifestyle characteristics were collected through interviews, direct observation, or physical measurements. Smoking habits were recorded through data collection forms and interviewer-guided questionnaires. Clinical characteristics were obtained through direct measurements. The procedure was as follows: (1)

weight and height were measured after an 8-12 hours fast to calculate Body Mass Index (BMI). We took 5 mL of venous blood from each volunteer's median cubital vein. We centrifuged 3 mL of whole blood at 3,000 x g for 15 minutes. Serum samples were analyzed for blood sugar, triglycerides, urea, cotinine, IGF-1, IGFBP-3, and TGF-β levels (2). Urea concentrations were measured using a spectrophotometer. We measured levels of IGF-1, IGFBP-3, TGF-β, and cotinine using ELISA [25]. T regulatory cells (Tregs) counts were determined using flow cytometry [26].

Data analysis

Data were processed and presented descriptively, followed by bivariate analyses. We compared hematologic cell counts, temporary blood sugar, triglycerides, urea, cotinine, IGF-1, IGFBP-3, and TGF-β levels between active-smokers and non-smokers with independent t-test, with statistical significance set at $p < 0.05$. We analyzed correlations between cotinine levels and IGF-1 and TGF-β using Pearson's correlation coefficient [27].

Research ethics

The local Institutional Review Board approved the study protocol. The study followed Good Clinical Practice. Study personnel explained the study's goal and objectives, expected benefits and uses, potential consequences, and participants' rights and obligations to all prospective participants. Written informed consent was obtained from each participant before enrollment. The study protocol and interview guidelines were reviewed and approved by the Health Research Ethics Committee, Faculty of Medicine, Public Health, and Nursing, Gadjah Mada University (ref No: KE/FK/847/EC).

Results

Subject characteristics

Subjects resided in both urban and rural areas across the five regencies of Daerah Istimewa Yogyakarta province. Based on Table 1, it is known that most participants were male, older than 45 years, had only elementary school education, and lived in rural areas. Their mean blood sugar levels (107.20 ± 37.94 mg/dL), triglycerides (122.25 ± 70.30 mg/dL), and urea (37.54 ± 38.02 mg/dL) remined within normal limits. Overall, 33.96% of participants were smokers, most of whom were private-sector workers, self-employed, and married.

Based on biomarker data from 106 participants, several findings suggested a trend toward accelerated biological aging. Triglyceride levels averaged 122.25 ± 70.30 mg/dL, remaining below the clinical thresholds (< 150 mg/dL). However, the substantial standard deviation indicated the presence of a subgroup with adverse metabolic profiles, such as insulin resistance or metabolic syndrome—conditions commonly associated with metabolic aging. The mean IGF-1 level (71.88 ± 26.09 ng/mL) was considerably below the expected range for middle-aged adults (100–200 ng/mL), indicating reduced anabolic and regenerative function. This decline is associated with impaired tissue repair, muscle wasting, and increased vulnerability to metabolic and degenerative diseases such as cardiovascular and chronic kidney disease. Although IGFBP-3 levels (1584.44 ± 706.68 ng/mL) were within the general reference range, they were relatively low compared to normative median values. Since IGFBP-3 regulates IGF-1 bioavailability, its suboptimal concentration supports the hypothesis of reduced endocrine anabolic activity.

The mean blood cotinine level was 19.14 ± 18.72 ng/mL, reflecting moderate to high exposure, compared with light-to-moderate active smoking. Chronic nicotine exposure has been shown to increase oxidative stress, suppress IGF-1 levels, stimulate TGF-β1 expression, and reduce both the number and function of regulatory T cells (Tregs).

Table 2. Profile of hemogram, blood chemistry, cotinine level, IGF-1, IGF-BP, and TGF-β based on smoking status.

Variable	Non-smoker (n = 75)	Active-smoker (n = 31)	Normal Reference	P
Hemoglobin	12.73 ± 1.89	13.22 ± 1.87	12.88 ± 1.89	0.2
Erythrocytes	4.53 ± 0.64	4.64 ± 0.54	4.56 ± 0.61	0.4
Leukocytes	9.63 ± 4.09	11.22 ± 5.80	10.09 ± 4.69	0.1
Platelet	262.46 ± 113.52	248.25 ± 88.03	258.31 ± 106.48	0.5
Hematocrit	38.25 ± 5.69	40.17 ± 5.71	38.81 ± 5.74	0.1
Random blood sugar (RBS)	107.48 ± 37.72	106.54 ± 39.09	107.20 ± 37.94	0.9
Triglycerides	123.39 ± 74.42	119.49 ± 60.19	122.25 ± 70.30	0.7
Urea	36.98 ± 40.67	38.88 ± 31.24	37.54 ± 38.02	0.8
Cotinine	9.70 ± 4.20	41.97 ± 20.54	19.14 ± 18.72	0.000*
IGFbp-3	1408.94 ± 620.63	2009.04 ± 731.06	1584.44 ± 706.68	0.000*
IGF- 1	78.84 ± 22.23	55.06 ± 27.39	71.88 ± 26.09	0.000*
TGF-β	167.48 ± 104.54	238.60 ± 89.02	188.28 ± 104.99	0.001*

Note: **Correlation is significant at the 0.01 level. *Correlation is significant at the 0.05 level.

Table 3. Levels of IGF-1 and TGF-β based on smoking and sex, age, and regency (living area) of healthy volunteers in Yogyakarta.

Characteristic		IGF-1		TGF-β	
		Smoker	Non-smoker	Smoker	Non-smoker
Sex	Men	55.05 ± 27.39	78.03 ± 24.25*	238.60 ± 89.54	184.35 ± 105.23*
	Women	-	79.80 ± 19.83		149.21 ± 101.34
	P	-	>0.05	-	> 0.05
Age (year)	< 60	52.01 ± 23.93	76.42 ± 20.11*	233.30 ± 88.79	168.90 ± 99.32*
	≥60	65.51 ± 37.31	85.06 ± 26.46*	256.78 ± 94.38	163.83 ± 118.06*
	P	>0.05	>0.05	> 0.05	> 0.05
Places	Urban	52.65 ± 38.24	80.00 ± 17.23*	244.70 ± 89.64	159.13 ± 103.23*
	Rural	55.90 ± 23.54	78.18 ± 24.12*	236.48 ± 90.21	172.18 ± 105.42*
	P	> 0.05	> 0.05	> 0.05	> 0.05

Note: **Correlation is significant at the 0.01 level. *Correlation is significant at the 0.05 level.

This combination contributes to cellular senescence, fibrosis, and chronic inflammation. TGF-β1 levels were markedly elevated (188.28 ± 104.99 ng/mL), exceeding the upper reference limit (~70 ng/mL) and suggesting systemic activation of profibrotic and pro-senescent pathways. This elevation indicated chronic inflammation, extracellular matrix accumulation, and immune suppression—key features of pathological aging. The absolute Treg count was also low (25.02 ± 7.37 cells/μL), well below the healthy adult reference range (50–120 cells/μL), indicating reduced immunoregulatory capacity. This decrease implies compromised immune tolerance and increased risk of autoimmunity, supporting the concept of "inflammaging," a hallmark of chronic low-grade inflammation during aging. The average blood urea level (37.54 ± 38.02 mg/dL) showed high inter-individual variability. Although the mean was within normal limits, the wide standard deviation suggests the presence of a subgroup with mild renal dysfunction, potentially linked to elevated TGF-β1 levels and age-related renal decline. The biomarker profile indicated a pattern of accelerated biological aging, characterized by high nicotine exposure, suppressed IGF-1 and Treg levels, and increased TGF-β1 expression. These findings underscore a decline in immune regulation and regenerative capacity, accompanied by increased tissue fibrosis.

Hemogram profile, blood chemistry, levels of IGF-1, IGFBP-3, and TGF-β based on smoking status

Table 2 presents a comparative analysis of hematological, biochemical, and aging-related biomarkers—including IGF-1, IGFBP-3, and TGF-β1—between active smokers and non-smokers. Several significant differences were observed, indicating the impact of cigarette smoke exposure on oxidative stress pathways and aging mechanisms. Active smokers exhibited markedly higher cotinine levels (41.97 ± 20.54 ng/mL) compared to non-smokers (9.70 ± 4.20 ng/mL; $P < 0.001$), consistent with light-to-moderate smoking behavior.

Levels of IGF-1 and TGF-β1 based on smoking status, gender, age, and location of residence

Table 3 presents IGF-1 and TGF-β1 levels in smokers and non-smokers, stratified by sex, age, and residential setting (urban *vs*. rural), to examine the molecular impact of cigarette smoke exposure on aging-related pathways. IGF-1 levels were lower in male smokers (55.05 ± 27.39 ng/mL) compared to non-smokers (78.03 ± 24.25 ng/mL). Among participants under 60 years, smokers had reduced IGF-1 levels (52.01 ± 23.93 ng/mL) compared to non-smokers (76.42 ± 20.11 ng/mL). Similarly, urban smokers had lower IGF-1 concentrations (52.65 ± 38.24 ng/mL) than their non-smoking counterparts (80.00 ± 17.23 ng/mL). However, the differences in IGF-1 and TGF-β levels based on gender, age, and region of origin were not statistically significant.

The relationship between Cotinine levels, IGF-1, and TGF-β

Table 4 shows associations between cotinine levels and IGF-1 and TGF-β levels. A strong and significant negative correlation was observed between cotinine and IGF-1 levels (r = –0.608; Cotinine correlated negatively with IGF-1 (r = -0.608, $P < 0.00$) and positively with TGF-β (r = 0.281, $P < 0.004$), indicating that higher cotinine concentrations were associated with lower IGF-1 levels and higher TGF-β1 levels. These findings are consistent with cotinine-mediated suppression of the GH/IGF-1 axis via oxidative stress and inflammation, which may impair neuroplasticity, reduce muscle mass, and accelerate cardiovascular and renal aging.

A moderate, significant positive correlation was found between IGF-1 and IGFBP-3 levels (r = 0.435; $P < 0.001$). The increase in IGFBP-3 may represent a compensatory response to declining IGF-1, but excessive IGFBP-3 can reduce IGF-1 bioavailability, promote cellular senescence, and activate the p53 and apoptotic pathways. A weak but significant positive correlation was noted between cotinine and TGF-β1 levels (r = 0.281; $P = 0.004$), suggesting that nicotine exposure may enhance TGF-β/Smad signaling, leading to fibrosis, immunosuppression, and

Table 4. Results of association analysis between cotinine, IGF-1, and TGF-β levels in healthy volunteers in Yogyakarta.

		Cotinine	IGF-1	IGFBP-3	TGF-β
Cotinine	Pearson Correlation	1	-0.608**	0.435**	0.281**
	Sig. (2-tailed)		0.000	0.000	0.004
IGF-1	Pearson Correlation	-0.608**	1	-0.473**	-0.371**
	Sig. (2-tailed)	0.000		0.000	0.000
TGF-β	Pearson Correlation	0.281**	-0.371**	0.238*	1
	Sig. (2-tailed)	0.004	0.000	0.014	

Note: **Correlation is significant at the 0.01 level. *Correlation is significant at the 0.05 level.

cellular senescence—hallmarks of accelerated biological and immune aging. A moderate negative correlation was observed between IGF-1 and IGFBP-3 ($r = –0.473$; $P < 0.001$), reflecting impaired tissue regeneration, reduced anti-apoptotic signaling, and disrupted cellular growth.

Discussion

This study presents novel evidence on the relationship between cigarette smoke exposure, serum cotinine levels, and biomarkers of aging—specifically insulin-like growth factor-1 (IGF-1) and transforming growth factor-beta 1 (TGF-β1). The findings are particularly significant in Indonesia, which is experiencing a rapid rise in premature aging alongside persistently high smoking prevalence.

Prevalence of smokers, secondhand smokers, and cotinine levels

The proportion of active smokers within the study population (33.9%) closely reflects national prevalence rates, thereby supporting the external validity and representativeness of the sample [28]. The mean blood cotinine concentration was 19.14 ± 18.72 ng/mL—levels typically observed among individuals with moderate to high secondhand smoke exposure and comparable to those reported in light-to-moderate active smokers. Nevertheless, the analysis revealed a striking intergroup disparity. As shown in Table 3, serum cotinine concentrations in active smokers were nearly fourfold higher than those in non-smokers (41.97 ± 20.54 ng/mL *vs*. 9.70 ± 4.20 ng/mL), underscoring substantial systemic accumulation of tobacco-related toxicants in smokers [29, 30].

These findings strongly suggest that most non-smokers in this cohort were secondhand smokers, as evidenced by serum cotinine concentrations >1 ng/mL but <10 ng/mL, the threshold typically used to distinguish passive from active exposure. Cotinine has been well established as the principal biomarker for quantifying exposure to tobacco smoke because of its greater stability and specificity compared with nicotine itself [30, 31].

In the United States, recent estimates indicate that approximately 58 million individuals—including nearly 45% of children—remain exposed to secondhand smoke, predominantly in household settings. Alarmingly, such exposure is attributed to an estimated 40,000 deaths annually. The prevalence of secondhand smoke exposure is not uniformly distributed; it varies substantially by socioeconomic status and race/ethnicity, with disadvantaged populations disproportionately burdened [32, 33]. Similarly, in Indonesia, the national prevalence of active smoking among individuals aged ≥ 15 years is estimated at 33–34%, with a striking gender disparity (62–65% among men *vs*. < 5% among women). Household exposure to secondhand smoke remains alarmingly high, affecting 60–70% of households, and disproportionately impacting women and children. Findings from the Global Adult Tobacco Survey (GATS) Indonesia 2021 further confirm that Indonesia continues to rank among the countries with the highest prevalence of active smoking worldwide, especially among men [34, 35]. These findings are consistent with global reference values: the Centers for Disease Control and Prevention (CDC) consider serum cotinine concentrations above 10 ng/mL as a reliable biomarker of active smoking. In comparison, non-smokers typically exhibit serum cotinine values below 1 ng/mL. The World Health Organization (WHO) regards cotinine as the most specific and sensitive biomarker for assessing nicotine exposure due to its longer half-life than nicotine itself [30, 36]. The elevated cotinine levels observed in this study therefore not only reflect direct tobacco exposure but also highlight the biological plausibility of nicotine metabolites as key mediators of oxidative stress, inflammation, and subsequent cardiovascular and systemic pathologies. These results reinforce cotinine's validity as a robust biomarker of tobacco-related exposure and provide mechanistic insights into how chronic smoking contributes to accelerate aging and increased susceptibility to cardiovascular disease, chronic kidney disease, immune dysfunction, and cancer [37, 38]. Collectively, these findings reinforce the urgent need to examine the molecular consequences of chronic cigarette smoke exposure. Nicotine, a primary bioactive compound in tobacco smoke, exerts harmful effects across multiple organ systems. It promotes oxidative stress, systemic inflammation, and vascular dysfunction—hallmarks of accelerated biological aging.

Effect of smoking behavior on IGF-1 and TGF-β levels

Table 2 shows that smokers had lower IGF-1 levels and higher TGF-β levels than non-smokers. The mean IGF-1 level among active smokers (55.06 ± 27.39 ng/mL) was significantly lower than that among non-smokers (78.84 ±

22.23 ng/mL; $p < 0.001$), and far below the normal reference range for middle-aged adults (100–200 ng/mL). This decline indicates diminished anabolic and regenerative capacity and elevated risk for degenerative diseases. Nicotine is known to induce oxidative stress, suppress IGF-1, and upregulate TGF-β1, collectively accelerating cellular senescence, fibrosis, and chronic inflammation [39].

Interestingly, Table 2 also shows that active smokers had significantly higher IGFBP-3 levels (2009.04 ± 713.06 ng/mL) than non-smokers (1408.94 ± 620.63 ng/mL; $p < 0.001$). This increase may represent a compensatory mechanism in response to reduced IGF-1 levels. However, elevated IGFBP-3 can also sequester free IGF-1, further impairing its bioactivity and contributing to metabolic dysregulation associated with aging [40]. TGF-β1 levels were also significantly higher in active smokers (238.60 ± 89.02 ng/mL) than in non-smokers (167.48 ± 104.54 ng/mL; $p = 0.001$), indicating upregulation of profibrotic and pro-aging signaling. TGF-β1 is a cytokine involved in fibrosis, cellular senescence, and immune suppression. Its excessive elevation reflects systemic activation of these pathways. No statistically significant between-group differences were found in hemoglobin, leukocyte count, platelet count, random blood glucose, triglycerides, or blood urea nitrogen levels. However, trends toward higher hematocrit and leukocyte counts in smokers may suggest mild inflammatory activation and subclinical dehydration [41].

We also conducted subanalyses by gender, age group, and geographic location (urban versus rural) to determine factors influencing changes in IGF-1 and TGF-β levels. There were differences in IGF-1 based on gender, age group, and geography, but these differences were not statistically significant. This decline reflects disruption of the GH/IGF-1 axis, likely due to chronic oxidative stress from smoke exposure, which impairs tissue repair, reduces muscle mass, and accelerates biological aging. TGF-β1 levels were consistently elevated in smoker groups, particularly among males (238.60 ± 89.54 *vs*. 184.35 ± 105.23 ng/mL), participants under 60 years (233.30 ± 88.79 *vs*. 168.90 ± 99.32 ng/mL), and urban residents (244.70 ± 89.64 *vs*. 159.13 ± 103.23 ng/mL). However, Table 3 shows that IGF-1 and TGF-β levels did not differ significantly based on gender, age group, or geographic location. Taken together, the results indicate that smoking status, rather than gender, age, or residence, was the primary factor associated with alterations in IGF-1 and TGF-β1 levels.

Cigarette smoking has been consistently documented as a significant risk factor for cellular damage, chronic inflammation, and the disruption of physiological homeostasis, ultimately contributing to the development of age-related diseases. Nicotine and other toxic compounds in cigarette smoke generate excessive reactive oxygen species (ROS), leading to oxidative stress that can overwhelm endogenous antioxidant defenses. This persistent oxidative stress induces lipid peroxidation, DNA damage, and protein modification, impairing cellular integrity and accelerating senescence [42]. Acute nicotine exposure has been shown to cause vasoconstriction in both the coronary and renal vasculature, increasing renal vascular resistance and reducing glomerular filtration rate (GFR), which may contribute to subclinical renal impairment observed in long-term smokers [43]. TGF-β1 is a key mediator of fibrosis, chronic inflammation, and cellular senescence. Its upregulation—driven by nicotine-induced activation of the TGF-β/Smad signaling pathway—promotes structural tissue changes and impairs regenerative function, contributing to accelerated aging. Although IGFBP-3 data are not shown in Table 3, previous data have shown elevated levels in smokers. While potentially compensatory for reduced IGF-1, high IGFBP-3 may decrease the availability of free IGF-1, exacerbating metabolic dysregulation. This imbalance between IGF-1 and IGFBP-3 reinforces pro-aging signals and supports chronic inflammatory mechanisms (inflammaging). Overall, our data demonstrate that cigarette smoke exposure is associated with lower IGF-1 and higher TGF-β1 across population subgroups. This biomarker profile indicates activation of oxidative stress and pro-aging molecular pathways, which may accelerate biological aging and increase the risk of degenerative diseases such as cardiovascular disease, kidney dysfunction, cancer, and immune impairment [44].

Association between cotinine, IGF-1, and TGF-β

The findings of this study demonstrate a clear association between serum cotinine levels and key biomarkers of cellular aging. Elevated cotinine, as an indicator of nicotine exposure, was significantly associated with a reduction in circulating IGF-1 levels, supporting the hypothesis that smoking disrupts anabolic signaling pathways. In particular, active smokers exhibited markedly lower IGF-1 concentrations than non-smokers, with a strong negative correlation between cotinine levels and IGF-1 ($r = –0.608$, $p < 0.001$). This reduction in IGF-1 is clinically relevant, as diminished IGF-1 activity has been linked to impaired cellular repair mechanisms, reduced proliferation, and accelerated senescence.

In parallel, IGF-1 levels negatively correlated with TGF-β1 ($r = –0.371$; $p < 0.001$), suggesting that nicotine exposure may drive a biological shift toward a profibrotic and pro-aging state. The concomitant weak yet significant positive correlation between IGFBP-3 and TGF-β1 ($r = 0.238$; $p = 0.014$) further underscores the complex interplay between growth factor regulation and fibrogenic pathways. Together, these findings highlight a disrupted IGF-1/IGFBP-3/TGF-β axis under nicotine exposure, potentially mediated through oxidative stress, chronic inflammation, and molecular mechanisms of aging. These correlations provide mechanistic insights into how nicotine may accelerate biological aging and promote susceptibility to chronic diseases. By altering growth factor signaling and enhancing profibrotic activity, nicotine contributes to the pathogenesis of cardiovascular disease, chronic kidney disease, immune dysregulation, and carcinogenesis, thereby reinforcing its role as a major determinant of morbidity and premature mortality. These findings highlight the intertwined impact of tobacco exposure on two key molecular players in aging and tissue homeosta-

sis: IGF-1 and TGF-β. Consistent with these results, active smokers exhibited significantly lower IGF-1 levels than non-smokers, with a strong negative correlation between serum nicotine and IGF-1 ($r = -0.608$, $P < 0.001$).

In contrast, TGF-β levels were markedly elevated in smokers, suggesting a shift in regulatory balance towards a profibrotic and immunosuppressive milieu. Insulin-like growth factor-1 (IGF-1) is pivotal in tissue regeneration, cellular survival, and metabolic regulation. The decline observed in smokers in this study reflects a state of anabolic resistance, likely driven by chronic oxidative stress, endothelial dysfunction, and inflammatory cascades initiated by tobacco constituents [45]. This decrease compromises multiple protective processes, including vascular relaxation, neuroprotection, and antioxidative defense, thereby accelerating biological aging and increasing susceptibility to age-related diseases such as CVD and neurodegeneration [22, 46].

Within this framework, the current study explored the correlations between nicotine exposure (as indicated by cotinine levels) and two critical aging biomarkers: IGF-1, which supports anabolic and regenerative processes, and TGF-β1, a central mediator of fibrosis, senescence, and immunosuppression [46]. Disruptions in the IGF-1/TGF-β1 axis may be early indicators of pathophysiological aging processes, particularly in metabolically active and vascular tissues [47]. Given the rising prevalence of early-onset chronic disease and frailty among Indonesia's adult population, identifying molecular signatures of aging in relation to modifiable risk factors such as smoking is essential [48]. These findings may inform preventive strategies and policy frameworks aimed at mitigating the impact of tobacco on aging and age-related diseases. These findings are consistent with previous literature indicating that smoking interferes with anabolic and protective signaling pathways in the body. IGF-1, a central anabolic hormone, plays a vital role in cell growth, differentiation, and survival, as well as metabolic regulation, antioxidative defense, and tissue repair [16, 26, 49].

In the cardiovascular system, IGF-1 contributes to vasorelaxation by modulating endothelial nitric oxide synthase (eNOS) and inducible nitric oxide synthase (iNOS), as well as the sodium/potassium ATPase pump [13]. The observed decline in IGF-1 in smokers is thus clinically relevant, as it reduces vascular resilience, promotes apoptosis, and increases susceptibility to atherosclerotic and degenerative changes. Reduced serum IGF-1 levels have been independently associated with increased cardiovascular and cerebrovascular disease risk. From a geroscience perspective, suppression of IGF-1 signaling due to chronic nicotine exposure represents a key mechanism of accelerated aging [50]. IGF-1 is critical for maintaining homeostasis in various tissues; its reduction contributes to sarcopenia, endothelial dysfunction, impaired neurogenesis, and immunosenescence [25]. The convergence of these processes results in heightened vulnerability to age-related diseases and premature mortality. Therefore, preserving IGF-1 signaling may represent a promising strategy in mitigating the pro-aging effects of tobacco exposure [39, 45].

TGF-β is a multifunctional cytokine involved in embryogenesis, wound repair, immune homeostasis, and inflammation [22]. Its signaling via Smad-dependent and Smad-independent pathways orchestrates complex cellular responses, including growth arrest, differentiation, and fibrosis [18, 51]. In this study, the elevated TGF-β levels among smokers reflect a shift toward a pro-aging, profibrotic phenotype [52]. Chronic nicotine exposure stimulates TGF-β production through ROS generation and NF-κB activation, contributing to tissue remodeling and dysfunction [53]. The imbalance between suppressed IGF-1 and elevated TGF-β signaling in smokers represents a molecular hallmark of premature aging. While IGF-1 promotes regenerative and protective signaling, TGF-β promotes senescence, fibrosis, and immune suppression. Tobacco smoke, rich in oxidants and toxic chemicals, perturbs this balance and fosters a systemic environment conducive to aging and chronic pathology. These findings align with broader literature demonstrating that long-term tobacco use induces mitochondrial dysfunction, telomere shortening, and senescence-associated secretory phenotype (SASP), which together converge on accelerated aging [22, 54]. Understanding the dual modulation of IGF-1 and TGF-β by nicotine may provide insight into novel therapeutic targets for mitigating tobacco-related tissue damage and aging. Pharmacologic interventions that restore IGF-1 signaling or attenuate TGF-β overactivation may reduce cardiovascular, renal, and fibrotic disease burden in smokers and aging populations [55].

Conclusions

The significant reduction of IGF-1 and concomitant elevation of TGF-β in smokers reflect a pathogenic shift toward a systemic pro-aging, pro-inflammatory, and profibrotic internal environment. The inverse correlation between serum cotinine and IGF-1 ($r = -0.608$) and the positive correlation between serum cotinine and TGF-β ($r = 0.281$) reinforce the mechanistic association between smoking and accelerated biological aging.

Nicotine (as reflected by serum cotinine) exerts its effect by inducing oxidative stress and inflammation, which suppress IGF-1 signaling—vital for vascular health, neuroprotection, and antioxidative defense. It also upregulates TGF-β expression through Smad-dependent and Smad-independent pathways, promoting fibrosis, immune suppression, and senescence.

Declarations

Authors contributions: Made substantial contributions to conception and design of the study, and performed data analysis and interpretation: Hidayati T, Akrom A, Sun S; Performed data acquisition, as well as provided administrative, technical, and material support: Hidayati T, Akrom A; Data analysis, drafting, and proofreading: Hidayati T.,

Akrom A, Sun S.

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Conflicts of interest: All authors declared that there are no conflicts of interest.

Ethical approval and informed consent: Research involving human subjects, material, or data must be performed per the Declaration of Helsinki and approved by an appropriate ethics committee. The study followed Good Clinical Practice, including explaining all potential subjects on the research's goal and objective, the expected benefits and uses, the consequences for them, and their rights and obligations as subjects. Written informed consent was obtained from each subject before they could participate. The study protocol and interview guidelines have been reviewed and approved by the health research ethics committee, Medical Faculty of Gadjah Mada University (ref No: KE/FK/847/EC).

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