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Original Research

Investigating serum levels of IL-6 and TNF alpha, and the risk of thrombosis in newly diagnosed chemotherapy naïve obese cancer patients

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Abstract

Background: Obesity and cancer increase thrombosis risk. IL-6 and TNF-α, are key inflammatory cytokines, which may contribute to hypercoagulability in newly diagnosed, chemotherapy-naïve obese cancer patients, warranting further investigation. This study aimed to investigate the serum levels of these inflammatory biomarkers and risk of VTE in chemotherapy naïve obese cancer patients (CNOCPs).
Methodology: The study was cross-sectional analytical in design. The participants consisted of newly diagnosed patients with solid malignancies recruited from adult oncology clinics of a Nigerian tertiary hospital. They were grouped into two: case group (n = 37) consisting of chemotherapy naïve OCPs and control group (n = 63) consisting of chemotherapy naïve non-OCPs Patients were risk assessed using the Khorana scoring system. All the patients' serum samples were assayed by ELISA technique for IL-6 and TNF-α. History of VTE was obtained from the patients' case notes and by direct interviews with the patients.
Results: The mean age of the participants was 48.44±13.4 (range = 20 – 76) years, and the mean BMI was 26.80±6.3Kg/m^2. The mean levels of IL-6 and TNF-α were significantly higher in chemotherapy naïve OCPs than the controls (7.9 ± 1.2 vs. 6.5 ±1.2, $p < 0.001$ and 5.2 ± 2.3 vs. 4.1 ± 1.9, $p = 0.012$ respectively. Also, chemotherapy naïve OCPs had a three-fold higher risk of VTE than the controls (OR: 3.0; 95% CI: 1.1-7.5; p= 0.03).
Conclusion: The inflammatory biomarkers were significantly higher in chemotherapy naïve OCPs than the non-obese controls. Additionally, they are at higher risk of VTE. These findings could strengthen clinicians' disposition for prompt initiation of thromboprophylaxis in OCPs.

Keywords: Cancer; Inflammatory Cytokines; Obesity, Body Mass Index; Venous Thromboembolism.

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Introduction

Obesity is characterized by a body mass index (BMI) of 30 kg/m2 or higher and is linked to more serious consequences in cancer patients, including a greater likelihood of cancer recurrence, and death.[1] Nearly half of all people in the United States are now considered obese, and the prevalence of obesity is rising whereas approximately 15% of adults in Nigeria are estimated to be obese, reflecting a growing public health concern in the country.[2,3] Treatment of obese people presents special issues since they have distinct pharmacokinetics and physiology.

Obesity is linked to metabolic dysfunction and hyperinsulinemia, which increases insulin-like growth factor-1 (IGF-1) synthesis, promotes chronic inflammation and activates the Phosphoinositide 3-kinases (PI3Ks) and Mitogen-activated protein kinases (MAPKs) signaling pathways, encouraging the survival and multiplication of cancer cells.[4-6] The main cellular component of adipose tissue, the adipocyte, becomes dysfunctional as a result of obesity, and this dysfunction can cause the production of adipokines, cytokines, and metabolic products, which can enhance the development of cancers.[7,8]

Obesity and the chance of developing cancer are clearly related.[9] Globally, a study found that excess body weight accounted for approximately 3.9% of all cancers (544,300 cases).[10] Several malignancies, including colorectal, breast, uterine, esophageal, kidney, and pancreatic cancers are linked to having too much body fat, according to several studies.[11. 12] The precise mechanism by which obesity raises that risk is less apparent. According to some reports, visceral fat, which is the fat that surrounds the important organs, is mostly to blame for the inflammation that it causes.[13] The visceral fat, contributes to inflammation because the fat cells become enlarged and stressed, releasing signals that attract immune cells. These immune cells produce inflammatory molecules called cytokines, creating a state of chronic, low-grade inflammation throughout the body. [14]

Obesity increases cancer risk through several biological mechanisms involving adipose tissue dysfunction, metabolic dysregulation, and chronic inflammation. First, adipose tissue acts as an endocrine organ, releasing pro-inflammatory adipokines like leptin and TNF-α, which promote cell proliferation and inhibit apoptosis.[15] Secondly, obesity-induced hyperinsulinemia and elevated IGF-1 levels activate mitogenic pathways such as PI3K/AKT, enhancing tumor growth and survival.[16] Third, chronic low-grade inflammation driven by macrophage infiltration into adipose tissue stimulates oncogenic pathways like NF-κB and STAT3, fostering a tumor-supportive microenvironment.[17] These interconnected mechanisms collectively contribute to DNA damage, immune evasion, and angiogenesis, increasing the likelihood of cancer development in obese individuals.[18]

Systemic inflammation has been linked to an increase in the prevalence of colorectal adenomas, whereas local chronic inflammatory diseases, including inflammatory bowel disease, have been linked to an increased risk of colorectal cancer.[19] Elevated levels of interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and the inflammatory biomarker C-reactive protein (CRP) have been associated with obesity. These molecules are primarily produced by adipocytes and macrophages, which tend to accumulate in adipose-rich tissues and are also commonly found in the tumor microenvironment of various cancers.[20,21]

Obesity contributes significantly to thrombosis risk through chronic low-grade inflammation and associated metabolic changes. Elevated inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) upregulate procoagulant factors like tissue factor and plasminogen activator inhibitor-1 (PAI-1), promoting a hypercoagulable state.[22,23] This inflammatory milieu also leads to endothelial dysfunction, characterized by reduced nitric oxide availability[24] and increased adhesion molecule expression, which further favors thrombus formation.[23] Additionally, obesity-related adipokines, particularly leptin, enhance platelet activation and aggregation, amplifying the risk of both

venous and arterial thromboembolic events.[25] These mechanisms collectively explain the strong link between obesity and increased incidence of thrombosis, underscoring the need for targeted prevention and management strategies in obese populations.

Despite the well-established links between inflammation, cancer, obesity, and thrombosis,[26] limited data exist on the specific contribution of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) to thrombosis risk in chemotherapy-naïve, newly diagnosed obese cancer patients. As these patients have not yet undergone treatment, evaluating their baseline inflammatory profile offers a unique opportunity to identify early markers of thrombotic risk before confounding effects of chemotherapy arise. A clearer understanding of this relationship may improve risk stratification, inform targeted thromboprophylaxis, and ultimately reduce thromboembolic complications in this high-risk population.

Patients and Methods

Study design and participants

This was a cross-sectional study conducted at the University of Nigeria Teaching Hospital Ituku/Ozalla between June 2021 and May 2023. One hundred patients with a histological diagnosis of cancer were recruited as they presented to the oncology clinic. These patients were enrolled and categorized into non-obese (BMI < 30 kg/m^2) and obese (BMI ≥ 30 kg/m^2) groups according to WHO-criteria. The control group was non-obese patients with diagnosis of cancer. Participants were selected using a consecutive sampling technique.

Inclusion criteria

Patients who had a new diagnosis of solid cancer irrespective of the organ involved and aged above 18 years.

Exclusion criteria

Those who were currently on anti-inflammatory agents and anticoagulation for VTE were excluded.

Ethical consideration

This was obtained from the University of Nigeria Teaching Hospital Enugu's institutional review board (UNTH/HREC/2021/03/84). All individuals provided their written informed consent before participating, and the study was conducted in accordance with the ethical principles of Helsinki declaration.

Sample size estimation

The sample size for this study was calculated using G-Power Software Version 3.1.9.7. Following the above calculation, a minimum of 34 participants per group was required to achieve 95% power at an alpha level of 0.05. Assuming an attrition rate of 10 %, the minimum sample size (n) was calculated to be 37 participants for each arm of the study.

Sample collection and measurement of serum IL-6 and TNF-alpha

The patients' venous blood samples were collected into plain bottles. The samples were allowed to stand for one hour for them to clot and retract before they were centrifuged at 1200 g for 10 min at 4°C. The serum samples were taken from the supernatant and stored at -80°C until time for the assay. QuicKey Pro Human IL-6 (Interleukin 6) and TNF-alpha ELISA Kits - Elabscience™ USA were used following the manufacturer's instructions to determine the serum concentrations.

Definitions

Khorana score was assigned to five clinical and pre-chemotherapy laboratory parameters: primary tumour site (+1 or 2 points), platelet count ≥ 350x109/L (+1 point), Hb ≤ 10g/dL or use of erythropoiesis-stimulating agents (+1 point), leukocyte count ≥ 11x109/L (+1 point), and BMI ≥ 35 kg/m^2 (+1 point). A sum score of 0 points classifies the patient as low risk of VTE, 1 or 2 points as intermediate risk, and ≥ 3 points as high risk of VTE.[27]

Statistical analysis

Descriptive statistics were calculated to assess the sociodemographic characteristics of the subject. All analyses were performed using the Statistical Package for Social Sciences (version 25.0, SPSS Inc., Chicago USA). Student's t-test for independent samples was used to compare the age, BMI and serum cytokines between the two groups while Chi square was used to compare the sex, history of deep venous thrombosis and history of previous surgery between the obese and non-obese cancer patients. The relationships were expressed using odds ratio and 95% confidence interval. A p value of < 0.05 was considered statistically significant.

Results

There were 100 patients (40 males and 60 females) with newly diagnosed cancers (chemotherapy naïve). The mean age was 48.4±13.4 years with a range of 20 to 76 years. Thirty-seven percent (37/100) were obese while 63% (68/100) were non-obese. The mean BMI was 26.8±6.3kg/m^2. Details of the sociodemographic characteristics of the patients including their age, sex, occupation, and educational status were as illustrated in Table 1.

The clinical parameters among OCP showed that 9/37 (24.3%) had a previous history of deep venous thrombosis while 13/37 (35.1%) had at least a previous surgery. Details were shown in Table 2.

The mean serum levels of IL-6 and TNF-α were significantly higher in chemotherapy naïve OCPs than the controls (7.9 ± 1.2 vs. 6.5 ±1.2, $p < 0.001$ and 5.2 ± 2.3 vs. 4.1 ± 1.9, $p = 0.012$ respectively). Details of these associations were as shown in Table 3. The mean level of IL-6 and TNF-α in OCP with thrombosis were 7.27 ± 0.52 and 5.31 ± 0.68 respectively. Only one person had DVT from the non-obese group with mean levels of IL-6 and TNF-α (5.89 and 3.98 respectively). Furthermore, the mean serum levels of IL-6 and TNF-α were significantly higher in OCP with DVT than in those without DVT (7.24± 1.41 vs 6.54± 0.37, P =0.02 and 5.34±0.25 vs 4.28± 1.32, P =0.02 respectively). Further details of the association were shown in Table 4.

Following risk assessment for VTE using the Khorana scores and classifications, chemotherapy naïve OCPs had a three-fold higher risk of VTE than their chemotherapy naïve non-OCPs controls (OR: 3.0; 95% CI: 1.1-7.5; p= 0.03). Details were as shown in Table 5.

Table 1: Demographic characteristics of the chemotherapy naïve obese cancer patients versus chemotherapy naïve non-obese cancer patients*

Variables	Obese >30Kg/m2 n =37(%)	Non-Obese <30Kg/m2 n = 63(%)	P value
Age			
Mean age	50.9 ±10.85	48.2±11.9	0.26
<40	8(21.6)	20(31.7)	0.28
≥40	29(78.4)	43(68.3)	
Sex			
Male	14(37.8)	28(44.4)	0.52
Female	23(62.2)	35(55.6)	
Occupation			
Civil servants	18(48.7)	26(41.3)	0.69
Artisans	7(18.9)	10(15.9)	
Students	4(10.8)	12(19.0)	
Traders	8(21.6)	15(23.8)	
Education Status			
Informal	3(8.1)	5(7.9)	0.63
Primary	3(8.1)	9(14.3)	
Secondary	14(37.9)	17(27.0)	
Tertiary	17(45.9)	32(50.8)	

*Chi square for categorical variables; T test for discrete variables, P =p value

Table 2: Comparison of some clinical parameters among the obese versus non-obese patients with cancer*

Variables	Obese >30Kg/m2 n =37(%)	Non-Obese <30Kg/m2 n = 63(%)	P value
History of DVT			
Yes	9	1	0.0002
No	28	62	
History of surgery			
Yes	13	17	0.39
No	24	46	
History of Hypertension			
Yes	17	10	0.001
No	20	53	
History of Diabetes			
Yes	5	2	0.05
No	32	61	

*χ = Chi Square, p = p value

Table 3: Comparison of the mean levels of inflammatory markers among chemotherapy naïve obese cancer patients versus chemotherapy naïve non-obese cancer patients

	Obese (BMI 30 and above (n=37)	Non obese (n=63)	T	P	CI
IL-6 (pg/ml)	7.88 ± 1.18	6.45 ±1.21	5.76	0.0001	0.94 to 1.92
TNF-α (pg/ml)	5.19 ± 2.27	4.12 ± 1.87	2.55	0.012	0.24-1.90

t = T test, p = p value, CI = Confidence interval

Table 4: Comparison of the mean levels of inflammatory markers among chemotherapy naïve obese cancer patients with DVT and those without DVT

	Obese with DVT (n=9)	Obese No DVT(n=28)	T	P	CI
IL-6 (pg/ml)	7.24± 1.41	6.54± 0.37	2.44	0.0198	0.12-1.28
TNF-α (pg/ml)	5.34± 0.25	4.28± 1.32	2.37	0.0232	0.15 -2.00

t = T test, p = p value, CI = Confidence interval, DVT = Deep venous thrombosis

Table 5: Risk assessment of the chemotherapy naïve obese cancer patients versus chemotherapy naïve non-obese cancer patients using Khorana Scoring system and classifications

Risk Category (scores)	Obese n=37	Non-Obese n=63	OR	95% CI	P value
High risk (≥ 3	13(35.14%)	10 (15.87%)	2.8	1.1-7.5	0.03*
Intermediate risk (1-2)	17(45.95%)	45 (71.43%)			
Low Risk (0)	7(18.92%)	8 (12.70%)			

OR= odds ratio; CI = Confidence interval; *= significant at p<0.05

Discussion

This study showed that obese patients with newly diagnosed cancer have significantly higher mean serum levels of inflammatory cytokines –interleukin -6 and tumour necrosis factor-alpha. This was similarly reported in a study by Divella et al who noted an increased production of inflammatory cytokines in obese patients.[28] IL-6 levels in cancer patients have been reported to be 2-fold to 10-fold higher as compared to the noncancer patients.[29] Another study observed that Serum levels of IL-6 and TNF-α correlates with clinicopathological features and patient survival in patients with prostate cancer and may act as predictors of progressive disease.[30]

We observed a notably higher prevalence of deep vein thrombosis (DVT) and comorbidities such as hypertension and diabetes among obese cancer patients. These comorbid conditions are known contributors to a prothrombotic state, consistent with earlier studies which report that obesity increases the risk of thromboembolic complications in cancer patients through multiple pathways, including endothelial dysfunction and altered fibrinolysis.[31, 32] Some studies carried out among outpatients and newly discharged patients identified obesity as an independent risk factor for VTE.[33, 34] In comparison to obesity alone, the risk of VTE was nearly doubled when obesity was combined with at least one of the risk variables substantially linked with VTE.[31 35] Some of these risk factors including hypertension and diabetes were found to be significantly higher in OCPs than in the control from our study.

Furthermore, the mean serum levels of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) were significantly elevated in the obese group, and even more so among those with a history of DVT. These findings align with existing literature that show obesity is associated with a chronic inflammatory state that amplifies the risk of thrombosis in cancer. [22, 36] Elevated IL-6 and TNF-α levels have been implicated in promoting coagulation, platelet activation, and vascular inflammation, all of which are mechanisms that underlie cancer-associated thrombosis.[37] In order words, the combined effects of obesity with increased levels of pro-inflammatory cytokines were the likely factors that predisposed these patients to a higher risk of thrombosis as noted from this study.

The Khorana scoring system is used to identify ambulatory cancer patients who are at risk of thrombosis and thus may require prophylactic anticoagulation. [27,38] This study found that the intermediate group and the high-risk Khorana score group had a greater number of obese patients. There is a 3-fold risk of obese patients having a high-risk Khorana score than the non-obese chemotherapy naïve cancer patients. According to the risk assessment tool, patients that scored ≥ 2 points are candidates for thromboprophylaxis. These are patients in the intermediate and high-risk groups. This means that cancer patients with obesity should be risk assessed for other thrombotic risk factors that may predispose them to thrombosis.

Study limitations

This is a one-center study and thus the result findings may not be generalizable to the entire population. Also, the sample size is small, and this may affect the inferences drawn from the statistics. A larger sample size will increase the reproducibility of the work.

Conclusion

The inflammatory biomarkers were significantly higher in chemotherapy naïve OCPs than the non-obese controls. Additionally, the OCPs are at higher risk of VTE. These findings buttress the fact that a proper risk assessment for VTE should be done for obese cancer patients, and this could guide clinicians in prompt prophylactic treatment of thrombosis.

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