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Serum Lipids, Insulin-Like Growth Factor Binding Protein-3 and Treatment Outcomes in Women with and without Cervical Lesions in South Western Uganda: A Cohort Study

Frank Ssedyabane¹, Thomas C Randall², Deusdedit Tusubira³, Cesar M Castro^{4,5}, Josephine Nambi Najjuma⁶, Christopher Okeny¹, Doreen Nuwashaba¹, Hope Mudondo¹, Rogers Kajabwangu⁷, Joy Muhumuza⁷, Alexcer Namuli⁷, Joseph Ngonzi⁷

¹Department of Medical Laboratory Science, Mbarara University of Science of Science and Technology, Mbarara, Uganda; ²Department of Global Health and Social Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; ³Department of Biochemistry, Mbarara University of Science of Science and Technology, Mbarara, Uganda; ⁴Centre for Systems Biology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; ⁵Cancer Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; ⁶Department of Nursing, Mbarara University of Science of Science and Technology, Mbarara, Uganda; ⁷Department of Obstetrics and Gynecology, Mbarara University of Science of Science and Technology, Mbarara, Uganda

Correspondence: Frank Ssedyabane, Email fssedyabane@must.ac.ug

Purpose: There is a documented association between cervical cancer and metabolic syndrome. In this study, we determined the association between lipids, insulin-like growth factor binding protein-3 (IGFBP-3) and treatment outcomes for cervical lesions at Mbarara Regional Referral Hospital (MRRH) in south western Uganda.

Patients and Methods: In this prospective cohort study, we recruited 94 cases and 94 controls at the cervical cancer clinic of MRRH, and followed them for 12 months. Cases were confirmed with cytology and/or histology. With consent, we collected demographic data and measured lipids and IGFBP-3 both at baseline and after 12 months. The lipid profile was measured using a Cobas 6000 Chemistry Analyzer, whereas IGFBP-3 was measured using a MAGLUMI fully automated chemiluminescence immunoassay analyzer. Abnormal values for lipids were defined using WHO recommended cut-offs. IGFBP-3 concentrations were divided into two categories of low concentration (<3.29 µg/mL) and raised concentration (≥3.29 µg/mL). Statistical analyses were conducted in STATA version 17 using logistic regression analysis. A *p*-value of <0.05 was taken to be statistically significant.

Results: The average (mean ± SD) age of our participants was 38.7±8.2 years for controls and 34.5±7.8 years for cases. The average serum IGFBP-3 concentration was 3.769±1.098 µg/mL among cases with cleared lesions and 3.505±0.979 µg/mL among cases whose lesions persisted. A serum IGFBP-3 concentration of less than 3.291 µg/mL was likely to be associated with clearance of cervical lesions (AOR 1.65, *p*=0.67), although this was not statistically significant. A serum triglyceride concentration of 35–135 mg/dL was also likely to be associated with clearance of cervical lesions (AOR 2.41, *p*=0.46), although this was also not statistically significant.

Conclusion: Although not statistically significant, reduced serum concentrations of IGFBP-3 and triglyceride may be associated with clearance of cervical lesions. Lipid management may be of benefit in the treatment of cervical lesions.

Keywords: cervical intraepithelial neoplasia, cervical lesions, clearance, persistence, IGFBP-3

Background

By the year 2020, 770,828 incident cases of cervical cancer were being registered globally per year.¹ Moreover, cervical cancer was reported to be the second most common of all cancers in women aged between 15 and 44 years worldwide.^{1,2} Cervical cancer accounts for more than 270,000 deaths annually. Worryingly, over 85% of these deaths occur in less developed countries,^{3,4} particularly in sub-Saharan Africa.^{5,6} In East Africa, there were over 43 new cervical cancer cases

per 100,000 in the year 2014.⁷ Furthermore, the age-standardized incidence rate of cervical cancer in Uganda is said to be higher than global estimates (56.2 per 100,000 women).⁸

The cervical cancer screening program in Uganda employs a “screen and treat” approach, in which all those screened and found positive are immediately initiated onto a treatment pathway. Screening involves performing visual inspection with acetic acid (VIA) and Papanicolaou (Pap) smear cytological confirmation.⁹ For women who test negative on VIA or Pap smear cytology, the interval for rescreening recommended by the World Health Organization (WHO)¹⁰ ranges from 3 to 5 years. For women who test negative for human papilloma virus (HPV), screening should be repeated after 5 years. After repeated screening with negative results, even for older women, it is recommended that the screening interval can be prolonged to at least 5 years. The current treatment modalities for cervical cancer, including chemotherapy, radiotherapy, single-agent treatment, concurrent chemoradiotherapy, neoadjuvant chemotherapy before surgery and radiotherapy, combination treatment, and platinum and non-platinum-based therapies, are able to target the early stage of cervical cancer, advanced stages and recurrent cervical cancer, but the survival rates are highest for women with early-stage disease.¹¹ After undergoing treatment for cervical precancerous lesions, women should receive post-treatment follow-up testing after 12 months, as recommended by the WHO.¹⁰ At Mbarara Regional Referral Hospital (MRRH), patients who receive treatment for either precancerous or cancerous cervical lesions are asked to return for a post-treatment review visit after 6 weeks. They are also asked to return for a follow-up visit at 12 months post-treatment, although there are no published data on whether these women actually return.

Several factors play multiple roles in HPV infection, its persistence, the development of cervical lesions and their clearance or persistence following treatment.¹² Lipid profiles in patients with cervical cancer and healthy patients differ during the development and pathogenesis of the disease.¹³ The different lipid profiling is therefore a useful tool in monitoring cervical cancer patients. In the early stages of the disease, total cholesterol, triglycerides and low-density lipoprotein (LDL) are usually significantly higher, whereas high-density lipoprotein (HDL) is significantly lower compared with the levels in healthy women.¹⁴ In cervical cancer, the expression and activity of insulin-like growth factor binding protein-3 (IGFBP-3) is often altered. Elevated levels of IGFBP-3 in cervical cancer cells can promote tumor growth by enhancing cell survival and proliferation. In addition, IGFBP-3 has been found to interact with various signaling pathways involved in cancer progression.^{15–20}

Results from earlier studies indicate that reduced or increased levels of IGFBP-3 could be associated with cancers, especially those originating from epithelial and glandular tissues.^{21–24} Therefore, in this study our aim was to describe the association between lipids and IGFBP-3 and clearance or persistence cervical lesions among women attending and receiving care at the cervical cancer clinic of MRRH.

Materials and Methods

Study Design

This was a prospective cohort type of study, conducted from April 2022 to June 2023. Each patient was followed for 12 months. This cohort started with cases and respective unmatched controls. The cases were defined as those women with a positive VIA who were then confirmed, with either Pap smear cytology or histology, to have cervical intraepithelial neoplasia (CIN) (atypical squamous cells of undetermined significance [ASCUS], low-grade squamous intraepithelial lesion [LSIL] and high-grade squamous intraepithelial lesion [HSIL]). The controls were women who were negative for cervical intraepithelial lesions or malignancy. Our outcomes of interest were clearance or persistence of cervical intraepithelial lesions, while the exposures were serum concentrations of IGFBP-3 and lipids.

Study Setting

We conducted this study among women attending the cervical cancer clinic of Mbarara Regional Referral Hospital, a referral hospital located in rural south western Uganda. This health facility serves a population of approximately four million people.²⁵ This referral clinic receives an average of 300 women per month and operates five days every week. The clinic serves over 13 districts of the whole of south western Uganda plus nearby countries, including Rwanda, Burundi, Tanzania and the Democratic Republic of Congo. The clinic staff include several nursing staff, a gynecologist

and senior residents. This team is supervised by a gynecological oncologist. Screening tests routinely done at the clinic include VIA, colposcopy, conventional cytology and HPV DNA. Women diagnosed with premalignant lesions are treated immediately with cryotherapy and thermocoagulation; those with confirmed cervical cancer undergo gynecological cancer surgery or are referred to a higher level health facility (Uganda Cancer Institute) for radiotherapy and chemotherapy, according to their cancer stage and clinical findings. Following treatment, the patients are advised to return for review visits at 6 weeks and 1 year.

Sampling Method

We recruited cases using a purposive sampling method. Thereafter, we used the incidence density sampling method to obtain a control each time a case was identified. This process went on prospectively until the required sample size was obtained.

Sample Size Determination

For the prospective cohort, we used a study power of 80%, a two-sided confidence level ($1 - \alpha$) of 95%, and a case to control ratio of 1. We also considered a proportion of cases with metabolic syndrome of 40.99%²⁶ and a proportion of controls with metabolic syndrome of 18.8%.²⁷ These were fed into an online sample size calculator with the least extreme odds ratio of 3.0, a prevalence ratio of 2.2 and a prevalence difference of 22 (OpenEpi: Sample Size for X-Sectional, Cohort, and Clinical Trials). This gave a total of 76 cases and 76 controls after considering the module of Fleiss with continuity correction.²⁸ Factoring in an expected 15% attrition rate, the resultant sample size came to a minimum of 86 cases and 86 controls.

Data Collection

Demographic Data Collection

We collected demographic data using a validated questionnaire which was administered by a trained research assistant, a midwife at the cervical cancer clinic. After receiving their routine care, participants who consented were helped by the research assistants to fill in the questionnaire. Thereafter, venous blood was drawn. Data collected included variables such as age, region of residence, family planning use and type, human immunodeficiency virus (HIV) status, highest level of education, marital status, and history of blood pressure and diabetes. The study's principal investigator performed random daily supervisory checks on the procedures to ensure conformity to the study requirements and standards. This ensured validity as well as completeness of data.

Blood Collection

After provision of written informed consent and completion of the questionnaire, we collected 4 mL of venous blood aseptically by venipuncture from the mid-cubital vein, into plain Vacutainers (without anticoagulant). We labeled specimens with unique identification numbers (codes) and then allowed them to clot at room temperature, after which they were taken to the laboratory for centrifugation at 3000 rpm for 5 min, to separate serum from blood cells. The serum was then transferred into cryovial tubes using a micropipette.

Measurement and Interpretation of Serum Lipids

Non-fasting lipid concentrations were measured using a fully automated analyzer (Cobas 6000 Clinical Chemistry Analyzer; Roche Diagnostics International, Rotkreuz, Switzerland). All testing was performed following standard operating procedures. Serum lipid concentrations were interpreted as follows, using standard cut-off values: abnormal total cholesterol was defined as a concentration above 200 mg/dL, abnormal LDL was defined as a concentration above 100 mg/dL, abnormal triglyceride was defined as a concentration outside the range of 35–135 mg/dL and abnormal HDL was defined as a concentration outside the range of 35–55 mg/dL.

Measurement and Interpretation of Serum IGFBP-3 Concentration

IGFBP-3 was measured using MAGLUMI fully automated chemiluminescence immunoassay analyzer (MAGLUMI 2000; SNIBE Diagnostic, Shenzhen, China). The human IGFBP-3 solid-phase sandwich enzyme-linked immunosorbent

assay (ELISA) is designed to quantitatively measure the target protein bound between a matched antibody pair. A target-specific antibody is precoated in the wells of the microplate. When samples, standards or controls are added into these wells, they bind to the immobilized antibody. The sandwich is then formed by the addition of the second antibody. When a substrate solution is added, it reacts with the enzyme–antibody–target complex, which eventually produces a measurable signal. The intensity of this signal is directly proportional to the concentration of target protein present in the specimen.

MAGLUMI kits and samples were thawed to room temperature, and serum samples were carefully transferred into sample tubes. Tubes were then loaded into sample racks and the fully automated testing was started. All this was done while strictly adhering to the operating instructions of the MAGLUMI fully automated chemiluminescence immunoassay analyzer. We ran samples along with quality control materials, which included Control 1 (lot 15622031Q1) and Control 2 (lot 15622031Q2). We created two categories of IGFBP-3 concentration, divided along the mean concentration in controls. The first category was named reduced concentration (<3.29 $\mu\text{g/mL}$) while the second category was named raised concentration (≥ 3.29 $\mu\text{g/mL}$).

Data Management and Analysis

The principal investigator collected the data together with research assistants. Data were entered into an Excel spreadsheet (Microsoft Office Professional Plus 2013, version 15.0.4675.1003; Microsoft, USA). The data were then imported into STATA 17 (StataCorp, College Station, Texas, USA) software. Descriptive statistics were used to describe the population using frequencies, means \pm standard deviations (SDs) and median values for continuous variables. We used frequencies and proportions to describe categorical variables. We employed bivariate and multivariate logistic regression analysis to derive associations between serum IGFBP-3 and lipid concentrations and treatment outcomes for cervical lesions. Multivariate analysis was conducted after controlling for age, region of residence, family planning use and type, HIV status, highest level of education, marital status, and history of blood pressure and diabetes. We used odd ratios as measures of association with respective 95% confidence intervals. A *p*-value of <0.05 was considered to be statistically significant.

Eligibility Criteria

We included all women aged 21 years and above, who sought care at the cervical cancer clinic of MRRH during the time of the study, screened with either VIA or HPV DNA, who provided written informed consent to participate in the study, and were later confirmed positive or negative for a precancerous lesion (CIN). The current guidelines for cervical cancer screening dictate the minimum age for cervical cancer screening to be 21 years.

Results

We recruited a total of 188 participants, including 94 cases and 94 controls. The mean age of participants in the control group was 38.7 ± 8.2 years, while that of the case group was 34.5 ± 7.8 years. The difference in the mean age of cases and controls was statistically significant ($p < 0.001$). Thirty-eight percent (35/94) of controls and 48% (45/94) of cases had attained primary education as their highest level of education. More than half (59%, 54/94) of cases were active contraceptive users, of whom 81.5% (44/54) used hormonal methods, while 41% (38/94) of controls were active contraceptive users, of whom 87% (33/38) used hormonal methods, as shown in [Table 1](#).

Distribution of Baseline Serum IGFBP-3 and Lipid Concentrations Across Grades of Cervical Lesions

The average serum IGFBP-3 concentration among controls was 3.29 (± 1.01) while that of LSIL and HSIL cases was 3.49 (± 0.96) and 3.22 (± 0.72) respectively. More than half of all LSIL cases (64%, 52/81) had a raised serum IGFBP-3 concentration. Also, more than half of controls (55%, 52/94) had a raised serum IGFBP-3 concentration. This distribution was not statistically significant. A big proportion of LSIL cases (83%, 67/81) had normal serum triglyceride concentration

Table 1 Socio-Demographic Characteristics of Study Participants at Mbarara Regional Referral Hospital

Variable		Controls	Cases	Test	p-Value
		N=94	N=94		
		Frequency (%)†	Frequency (%)†		
Age (years)		38.67±8.23	34.53±7.79	Ind. t-test	<0.001**
Age group (years)	19–29	16 (17%)	24 (26%)	Fisher's exact	0.03**
	30–39	33 (35%)	42 (45%)		
	40–49	38 (40%)	27 (29%)		
	50–59	7 (7%)	1 (1%)		
Region of residence	Central	1 (1%)	2 (2%)	Fisher's exact	0.74
	Rest of South West Uganda	46 (49%)	49 (52%)		
	Mbarara city	47 (50%)	43 (46%)		
History of high BP	No	70 (74%)	74 (79%)	Chi-square	0.49
	Yes	24 (26%)	20 (21%)		
History of diabetes	No	79 (84%)	82 (87%)	Chi-square	0.53
	Yes	15 (16%)	12 (13%)		
Marital status	Single	14 (15%)	21 (22%)	Chi-square	0.43
	Married	60 (65%)	54 (57%)		
	Divorced	19 (20%)	19 (20%)		
Highest level of education	Never studied	13 (14%)	4 (4%)	Chi-square	0.013**
	Pre-primary	5 (5%)	3 (3%)		
	Primary	35 (38%)	45 (48%)		
	Secondary	34 (37%)	25 (27%)		
	Tertiary	5 (5%)	9 (10%)		
	University	1 (1%)	8 (9%)		
HIV status	Negative	52 (55%)	50 (53%)	Chi-square	0.56
	Positive	41 (44%)	44 (47%)		
	Unknown	1 (1%)	0 (0%)		
Smoking	No	93 (99%)	86 (92%)	Fisher's exact	0.035**
	Yes	1 (1%)	7 (8%)		
Contraceptive use	No	54 (59%)	37 (41%)	Chi-square	0.015**
	Yes	38 (41%)	54 (59%)		
Type of contraceptive	IUD	3 (8%)	8 (14.8%)	Chi-square	0.62
	Hormonal	33 (87%)	44 (81.5%)		
	Condom	2 (5%)	2 (3.7%)		
Baseline IGFBP-3 (µg/mL)		3.29±1.01	3.4±7.93	Ind. t-test	0.21
Baseline total cholesterol (mg/dL)		151.01±43.12	145.32±35.86	Ind. t-test	0.33
Baseline triglycerides (mg/dL)		121.39±59.59	94.96±50.68	Ind. t-test	0.001**
Baseline HDL (mg/dL)		45.29±8.25	44.20±8.04	Ind. t-test	0.36
Baseline LDL (mg/dL)		159.08±694.38	79.56±28.79	Ind. t-test	0.27

Notes: †Continuous variables (age, baseline IGFBP-3, baseline total cholesterol, baseline triglycerides, baseline HDL and baseline LDL) are presented as mean ±SD. **Statistically significant ($p \leq 0.05$).

Abbreviations: BP, blood pressure; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; IGFBP-3, insulin-like growth factor binding protein-3; IUD, intrauterine device; LDL, low-density lipoprotein.

compared with the 17% (14/81) who had abnormal triglyceride concentration. The overall distribution of serum triglyceride concentration across grades of cervical lesions was statistically significant ($p=0.009$), as shown in Table 2.

Treatment Outcomes at 12 Months Post-Treatment

Out of the 94 cases at baseline, only 50 returned for follow-up at 12 months, making a 12 months' loss to follow-up rate of 46.8%. Close to 90% (88%, 44/50) of all cases who returned for 12 months' follow-up were declared to have cleared their cervical lesions. A small proportion (12%, 6/50) had persistent lesions. The majority of cases with cleared cervical lesions (90%, 38/44)

Table 2 Distribution of Baseline Serum IGFBP-3 and Lipid Concentrations Across Grades of Cervical Lesions of Study Participants at Mbarara Regional Referral Hospital

Variable		ASCUS	HSIL	LSIL	NILM	Test	p-Value
		N=1	N=12	N=81	N=94		
		Frequency (%)	Frequency (%)	Frequency (%)	Frequency (%)		
IGFBP-3 (µg/mL)	Low	0 (0%)	6 (50%)	29 (36%)	42 (45%)	Fisher's exact	0.47
	Raised	1 (100%)	6 (50%)	52 (64%)	52 (55%)		
Total cholesterol (mg/dL)	<200	1 (100%)	12 (100%)	74 (91%)	83 (88%)	Fisher's exact	0.62
	≥200	0 (0%)	0 (0%)	7 (9%)	11 (12%)		
Triglycerides (mg/dL)	35–135	1 (100%)	8 (67%)	67 (83%)	58 (62%)	Fisher's exact	0.009**
	0–34/	0 (0%)	4 (33%)	14 (17%)	36 (38%)		
	≥136						
HDL (mg/dL)	35–55	1 (100%)	11 (92%)	76 (94%)	90 (96%)	Fisher's exact	0.59
	0–34/≥56	0 (0%)	1 (8%)	5 (6%)	4 (4%)		
LDL (mg/dL)	<100	1 (100%)	12 (100%)	62 (77%)	70 (74%)	Fisher's exact	0.2
	≥100	0 (0%)	0 (0%)	19 (23%)	24 (26%)		

Notes: All data are categorical, and are presented as frequency (proportion). **Statistically significant (p≤0.05).

Abbreviations: ASCUS, atypical squamous cells of undetermined significance; HDL, high-density lipoprotein; HSIL, high-grade squamous intraepithelial lesion; IGFBP-3, insulin-like growth factor binding protein; LDL, low-density lipoprotein; LSIL, low-grade squamous intraepithelial lesion; NILM, negative for intraepithelial lesions or malignancy.

had been treated with cryotherapy, while 50% (3/6) of those with persistent lesions had also been treated with cryotherapy. This observation was statistically significant (p=0.03). More than half (64%, 28/44) of all cases with cleared lesions were married. More than half (67%, 4/6) of all participants with persistent lesions were residing in other districts of south western Uganda, 50%

Table 3 Treatment Outcomes for Cervical Lesions at 12 Months Post-Treatment of Study Participants at Mbarara Regional Referral Hospital

Variable		Cleared	Persisted	Test	p-Value
		N=44	N=6		
		Frequency (%)	Frequency (%)		
Age group (years)	19–29	12 (27%)	2 (33%)	Fisher's exact	1
	30–39	18 (41%)	2 (33%)		
	40–49	14 (32%)	2 (33%)		
Region of residence	Central	19 (43%)	2 (33%)	Fisher's exact	0.73
	Rest of South Western Uganda	24 (55%)	4 (67%)		
	Mbarara city	1 (2%)	0 (0%)		
History of high BP	No	34 (77%)	4 (67%)	Fisher's exact	0.62
	Yes	10 (23%)	2 (33%)		
History of diabetes	No	36 (82%)	5 (83%)	Fisher's exact	1
	Yes	8 (18%)	1 (17%)		
Marital status	Single	7 (16%)	3 (50%)	Fisher's exact	0.17
	Married	28 (64%)	2 (33%)		
	Divorced	9 (20%)	1 (17%)		
Highest level of education	Never studied	3 (7%)	0 (0%)	Fisher's exact	0.17
	Pre-primary	0 (0%)	1 (17%)		
	Primary	21 (48%)	2 (33%)		
	Secondary	10 (23%)	3 (50%)		
	Tertiary	5 (11%)	0 (0%)		
	University	5 (11%)	0 (0%)		

(Continued)

Table 3 (Continued).

Variable		Cleared	Persisted	Test	p-Value
		N=44	N=6		
		Frequency (%)	Frequency (%)		
HIV status	Negative	18 (41%)	3 (50%)	Fisher's exact	0.69
	Positive	26 (59%)	3 (50%)		
Smoking	No	42 (95%)	5 (83%)	Fisher's exact	0.32
	Yes	2 (5%)	1 (17%)		
Contraceptive use	No	15 (36%)	3 (50%)	Fisher's exact	0.66
	Yes	27 (64%)	3 (50%)		
Type of contraceptive	IUD	3 (11%)	0 (0%)	Fisher's exact	1
	Hormonal	23 (85%)	3 (100%)		
	Condom	1 (4%)	0 (0%)		
Treatment modality	Cryotherapy	38 (90%)	3 (50%)	Fisher's exact	0.03**
	Thermocoagulation	4 (10%)	3 (50%)		

Notes: All data are categorical variables, and are presented as frequency (proportion). **Statistically significant ($p < 0.05$).

Abbreviations: BP, blood pressure; HIV, human immunodeficiency virus; IUD, intrauterine device.

(3/6) were single and 50% were contraceptive users (3/6). More than half (59%, 26/44) of all cases with cleared lesions were HIV positive, as shown in Table 3.

Distribution of Follow-Up Serum IGFBP-3 and Lipid Concentrations Across Treatment Outcomes

The mean serum IGFBP-3 concentration among cases with cleared lesion was 3.77 ± 1.09 $\mu\text{g/mL}$, while it was 3.51 ± 0.98 $\mu\text{g/mL}$ among those cases whose lesions persisted after 12 months of post-treatment follow-up. More than half (68%, 30/44) of cases whose lesions cleared had raised IGFBP-3 serum concentrations after 12 months of post-treatment follow-up. An equally large proportion (67%, 4/6) of cases whose lesions persisted had raised IGFBP-3 serum concentrations after 12 months of post-treatment follow-up. This observation was, however, not statistically significant. Half (50%, 22/44) of all participants who had cleared cervical lesions had an abnormal total cholesterol concentration. The same proportion (50%, 3/6) of all participants who had persistent cervical lesions had an abnormal total cholesterol concentration. More than half (67%, 4/6) of participants with

Table 4 Distribution of Follow-Up Serum IGFBP-3 and Lipid Concentrations Across Treatment Outcomes of Cervical Lesions of Study Participants at Mbarara Regional Referral Hospital

Variable		Cleared	Persisted	Test	p-Value
		N=44	N=6		
		Frequency (%)†	Frequency (%)†		
Total cholesterol (mg/dL)		191.61 \pm 27.89	187.67 \pm 31.31	Ind. t-test	0.75
Triglycerides (mg/dL)		124.71 \pm 29.19	119.18 \pm 40.88	Ind. t-test	0.68
HDL (mg/dL)		46.19 \pm 9.78	42.93 \pm 4.13	Ind. t-test	0.43
LDL (mg/dL)		120.09 \pm 25.82	120.33 \pm 26.12	Ind. t-test	0.98
Total cholesterol categories (mg/dL)	<200	22 (50%)	3 (50%)	Fisher's exact	1
	\geq 200	22 (50%)	3 (50%)		
Triglyceride categories (mg/dL)	35–135	34 (77%)	4 (67%)	Fisher's exact	0.62
	0–34/ \geq 136	10 (23%)	2 (33%)		
HDL categories (mg/dL)	35–55	37 (84%)	6 (100%)	Fisher's exact	0.58
	0–34/ \geq 56	7 (16%)	0 (0%)		

(Continued)

Table 4 (Continued).

Variable		Cleared	Persisted	Test	p-Value
		N=44	N=6		
		Frequency (%)†	Frequency (%)†		
LDL categories (mg/dL)	<100	13 (30%)	2 (33%)	Fisher's exact	1
	≥100	31 (70%)	4 (67%)		
IGFBP-3 (µg/mL)		3.77±1.09	3.51±0.98	Ind. t-test	0.58
IGFBP-3 categories (µg/mL)	Low	14 (32%)	2 (33%)	Fisher's exact	1
	Raised	30 (68%)	4 (67%)		

Note: †Continuous variables (total cholesterol, triglycerides, HDL, LDL and IGFBP-3) are presented as mean±SD.

Abbreviations: HDL, high-density lipoprotein; IGFBP-3, insulin-like growth factor binding protein-3; LDL, low-density lipoprotein.

Table 5 Bivariate and Multivariable Logistic Regression Analysis Showing Associations Between Reduced Follow-Up Serum IGFBP-3 and Lipid Concentrations and Clearance of Cervical Lesions of Study Participants at Mbarara Regional Referral Hospital

Variable	Bivariate			Multivariate		
	COR	p-Value	95% CI	AOR	p-Value	95% CI
IGFBP-3 (µg/mL)	0.93	0.94	0.15–5.72	1.65	0.67	0.17–16.57
Total cholesterol (mg/dL)	1.00	0.74	0.98–1.04	0.82	0.84	0.11–5.93
Triglycerides (mg/dL)	1.70	0.57	0.27–10.68	2.41	0.47	0.23–25.69
HDL (mg/dL)	1			1		
LDL (mg/dL)	0.84	0.84	0.14–5.16	0.82	0.85	0.10–6.71

Note: All data are presented after controlling for age, region of residence, family planning use and type, HIV status, highest level of education, marital status, history of blood pressure and history of diabetes.

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; COR, crude odds ratio; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; IGFBP-3, insulin-like growth factor binding protein-3; LDL, low-density lipoprotein.

persistent cervical lesions had abnormal LDL concentration as well as an abnormal triglyceride concentration. However, none of the lipids showed any statistically significant distribution across treatment outcomes, as shown in [Table 4](#).

Association Between Follow-Up Serum IGFBP-3 and Lipid Concentrations and Clearance of Cervical Lesions

After controlling for age, region of residence, family planning use and type, HIV status, highest level of education, marital status, and history of blood pressure and diabetes, we found that a serum IGFBP-3 concentration of less than 3.291 µg/mL is likely to be associated with clearance of cervical lesions (adjusted odds ratio [AOR] 1.65, $p=0.67$, 95% confidence interval [CI] 0.17–16.57), although this was not statistically significant. We also found that a serum triglyceride concentration of 35–135 mg/dL is likely to be associated with clearance of cervical lesions (AOR 2.41, $p=0.46$, 95% CI 0.23–25.69), although this was also not statistically significant, as shown in [Table 5](#).

Discussion

We present results showing a trend towards a likely association between reduced serum IGFBP-3 and triglyceride concentrations and clearance of cervical lesions among our study population, although this was not statistically significant. To our knowledge, this is the first study in Uganda to examine the possible association between serum lipids and IGFBP-3 concentrations and treatment outcomes for cervical lesions.

We did not find any statistically significant associations between baseline IGFBP-3 concentration or its categories and cervical intraepithelial lesions among study cases and controls. Previous work by Wu et al²⁹ demonstrated that serum

IGFBP-3 was significantly higher in groups with CIN compared to controls. This difference could be explained by the fact that our IGFBP-3 concentrations were not necessarily raised above normal ranges (0.63–10.2 µg/mL). Our categorization was based on the mean serum concentration in controls. In agreement with our finding, Lee et al³⁰ found no association between CIN and serum IGFBP-3 levels. IGFBP-3 as a binding protein is said to have the ability to play a dual role. IGFBP-3 can inhibit cell proliferation and accelerate apoptosis in a manner that is insulin-like growth factor (IGF)-dependent or IGF-independent. However, it is worth noting that in situations of high IGF-1 concentration, as it could be in our case, IGFBP-3 can synergize the effects of IGF. It can present and release IGF-1 for interaction with its receptor, while at the same time protecting the receptor from down-regulation by exposure to high IGF-1 concentrations.³¹

The distribution of triglyceride concentrations across grades of cervical lesion was statistically significant ($p=0.009$). In our earlier studies in the same population,³² we demonstrated that dyslipidemia, especially triglyceride dyslipidemia, is a prevalent condition among this population. In agreement with our finding, studies on metabolic syndrome components have hypothesized that increased triglyceride concentrations can increase a person's risk of developing not only cardiovascular diseases but also other non-communicable diseases, including cervical cancer.³³ Research by Bumrungrathai et al³⁴ indicates that an abnormal serum triglyceride concentration is associated with an increased risk of development of cervical precancerous lesions. Dyslipidemia, in common with other components of metabolic syndrome such as obesity, elevates estrogen levels,³⁵ which, in turn, can increase the risk of HPV infection.^{36,37}

We observed a 12 months' loss to follow-up rate of 46.8%. This is comparable to our previous finding of 76.2% at the same clinic.³⁸ Close to 90% of all cases had cleared cervical lesions. The majority of cases with cleared cervical lesions had been treated with cryotherapy. This concurs with earlier reports on the success rates of cryotherapy for the treatment of cervical precancerous lesions,³⁹ although more recent work by Randall et al⁴⁰ shows otherwise. Cryotherapy has been described as a simple, cheap, accessible, applicable and effective treatment modality for cervical precancerous lesions in developing countries.⁴¹ Most of the cases in this study had been diagnosed with CIN and received treatment, mostly with cryotherapy, and after 12 months they were confirmed to have cleared their lesions. A previous study by Luciani et al⁴² reported that cryotherapy effectively cured 418 women (88%) with cervical precancerous lesions, of whom 49 (70%) had a baseline diagnosis of cervical intraepithelial lesion grade 3. Although thermal ablation treatment modalities have been argued to have better treatment outcomes,⁴⁰ it is important to note that availability of a given treatment modality, and especially in the cervical cancer clinic of MRRH, is based on a number of factors, including equipment breakdown and supply shortages, as highlighted previously.⁴³

More than half (64%, 28/44) of all cases with cleared lesions were married. This also highlights the importance of social support in the treatment of cervical lesions. Previous studies have demonstrated that social support by family members or peers, or any other form of social support, is key to achieving positive treatment outcomes for malignancies.^{38,44–47} Also, more than half (59%, 26/44) of all cases with cleared lesions were HIV positive. A systematic review published in 2020 found that adequate facilitation, as is currently available for women living with HIV, and high compliance with antiretroviral therapy have a positive impact on cervical cancer treatment response.⁴⁸ It is worth noting that, in our setting, women living with HIV have more contact with the health system and benefit from more health information than do their HIV-negative peers.

We take note that more than half of cases with persistent lesions were residing in districts other than Mbarara and central Uganda. This reflects on the impact of socio-economic status⁴⁹ and distance from health facility^{50,51} on treatment outcomes, since central Uganda and Mbarara city are periurban areas compared to the rest of south western Uganda. Also, half of participants with persistent lesions were single. This may be explained by their relative perceived absence of social support, which is known to influence treatment outcomes of various disease conditions in married people.^{38,44–47}

We categorized IGFBP-3 along the mean concentration in controls (3.29 µg/mL) as raised (≥ 3.29 µg/mL) or reduced (< 3.29 µg/mL). Although it was not statistically significant, we present a finding that more than one-third (32%, 14/44) of cases with cleared lesions had reduced IGFBP-3 serum concentrations at 12 months post-treatment. This underscores the biochemical roles of IGFBP-3. IGFBP-3 is the primary transport protein for IGF-1, called somatomedin C in humans,⁵² and it binds to and regulates the effects of IGF-1, thereby inhibiting cell division and inducing apoptosis in various cell types in an IGF-1-independent manner.⁵³ This is because IGFBP-3 increases the ratio of proapoptotic to antiapoptotic

proteins and/or causes the activation of the cascades involved in a death receptor-mediated pathway,^{54,55} and hence the arrest of the cell cycle at the G1/S phase of cytokinesis, subsequently inducing apoptosis.⁵⁵ This is a negative response to the action of growth hormones and is beneficial in the arrest of unnecessary cytokinesis, such as in neoplasms.⁵² However, 68% of participants with cleared lesions also had raised IGFBP-3 levels. This elevation in post-follow-up serum IGFBP-3 could have inhibited the effects of IGF-1 (somatomedin C), thereby reverting the growth hormone effects and subsequently contributing to clearance of the cervical precancerous lesions.^{53,55}

We report increased proportions of abnormal lipids, namely total cholesterol, triglycerides, HDL or LDL, across the treatment outcomes, although these differences were not statistically significant. Metabolic syndrome components, including abnormal lipids, are said to act as cofactors in cervical carcinogenesis, as seen in the positive correlation between estrogen and adipokine levels in cancer of the cervix.^{56,57} Abnormal serum triglyceride and HDL concentrations are said to be risk factors for cervical cancer⁵⁸ and hence could be associated with poor treatment outcomes. They are known to accelerate the growth of cancer cells and induce antiapoptotic capacity via activation of the production of reactive oxygen species.⁵⁹ A previous study by Jiang et al¹⁴ demonstrated that total cholesterol, triglyceride and LDL serum concentrations are significantly higher in cervical cancer patients compared to controls. However, the same study revealed that HDL concentrations are lower in cervical cancer patients compared to controls. Similar distributions have been reported by Raju et al in an Indian population⁶⁰ and Tulinius et al in an Icelandic population.⁶¹ However, in agreement with our finding, Sun et al⁶² reported no significant differences in any lipid concentrations between cervical cancer patients and controls.

With a categorization of IGFBP-3 along the mean concentration in controls (3.29 µg/mL) as raised (≥ 3.29 µg/mL) or reduced (< 3.29 µg/mL), we present findings that show that a serum IGFBP-3 concentration of less than 3.29 µg/mL is likely to be associated with clearance of cervical lesions, although this result was not statistically significant. IGFBP-3 is the dominant among several circulating binding proteins for IGF-1.^{63,64} It has been shown to induce apoptosis⁶⁵ and its expression is involved in regulation of many tumors.⁶⁶ IGF-1 binds to IGFR-1, thereby activating the P13K/Akt pathway, which stimulates cell growth and blocks apoptosis.⁶⁵ Studies have suggested that increased concentrations of circulating IGF-1 are associated with an increased risk of cancer.^{63,67,68} However, significantly reduced IGFBP-3 concentrations have been shown to have an inverse relationship with the risk of cancers^{63,69,70} as well as tumor migration,^{71,72} leading to tumor growth and suppressed apoptosis.^{73,74} In addition, reduced IGFBP-3 concentrations could indicate a stronger immune system, which plays an important role in the suppression of tumors.

We also report that more than half of all participants with persistent cervical lesions had raised serum IGFBP-3. However, we were unable to perform statistical analyses between increased serum IGFBP-3 and the persistence of cervical lesions owing to the limited number of observations. There have been assertions that the overexpression of serum IGFBP-3 inhibits tumor growth and that it may be a laboratory marker of improved cancer survival.⁷⁵ It has also been said that IGFBP-3 has an inverse association with death due to cancer, although that research was on male subjects.⁷⁶

Previous work by Lee et al³⁰ found no significant association between CIN and serum IGFBP-3 levels. However, levels of circulating insulin-like growth factors have been said to vary with age,⁷⁷ increasing from birth to puberty and reducing thereafter. This could partly explain our finding. Most of our participants were beyond puberty and much older, and hence age may have affected this observation, as similarly reported previously.³⁰ We hypothesize that a number of factors in this population could be influencing these observations. For example, factors such as obesity have been thought to cause variations in IGFBP-3.⁷⁸ This could be true considering the fact that we demonstrated this population to have an increased body mass index.⁷⁹ Also, IGFBP-3 could be working along with other factors associated with persistence of cervical lesions. Immortalization of HPV-infected cells is a major factor in cervical carcinogenesis. It may be activated by inactivation of P53, a cell cycle regulator, through the effects of *E6* and *E7* genes.⁸⁰

We studied a population that was found to have comorbidities, including hypertension, HIV and diabetes. Some of these disease conditions have been thought to have an association with treatment outcomes for malignancies. For instance, patients with comorbidities such as diabetes tend to have poor treatment outcomes for any malignancy.^{81,82} Other population factors, including age, together with chronic diseases such as hypertension and diabetes, have been said

to be associated with inflammation, which is associated with the secretion of numerous cytokines, most of which promote tumor growth, eventually leading to poor treatment outcomes including the persistence of lesions.^{83,84}

We also observed a trend for reduced serum triglyceride concentrations to be associated with clearance of cervical lesions, although this observation was not statistically significant. This is in agreement with the findings of a number of previous studies. For instance, work by Lin et al⁸⁵ showed that total cholesterol and triglycerides are not only independent prognostic factors for cervical cancer in its early stages but also associated with poor survival. It is emphasized that high triglycerides and high cholesterol lead to increased efflux of proinflammatory cytokines and chemokines, which results in reduced immunity and eventually tumor growth and poor treatment outcomes, including persistence of lesions.⁸⁶ Another study, by Jiang et al,¹⁴ showed that a high triglyceride concentration is associated with worse treatment outcomes, especially in patients aged 50 years and above. However, only 1% of our participants were in the age bracket of 50–59 years.

Many of our participants with cleared cervical lesions also had abnormal lipids. This contradicts much of the available literature on the association between lipids and treatment outcomes. Because of this observation, we take note that carcinogenesis involves various pathways, mostly the catabolism to anabolism transition.⁸⁷ Therefore, participants may have abnormal lipids but then experience better treatment outcomes, including clearance of cervical lesions.

Our study has several limitations. We did not derive associations between raised IGFBP-3 or lipids and the persistence of cervical lesions. This is because we had fewer than 10 participants with persistent lesions and this could not support the derivation of associations using logistic regression. However, high triglycerides being a predictor of poor treatment outcomes is consistent with many previous studies in other cancers, including prostate and breast. According to findings by Allott et al,⁸⁸ increased serum triglyceride concentrations are associated with the recurrence of prostate cancer. A study of 5-year survival outcomes revealed that increased triglyceride concentrations are associated with decreased 5-year survival among breast cancer cases.⁸⁹ Similar findings have also been reported in neuroendocrine tumors.⁹⁰ Cancer cells are also known to require large amounts of lipids for a number of cellular functions, including cell membrane synthesis during increased cell growth and proliferation.⁹¹ In addition to the already known impact of HPV persistence on the recurrence of cervical lesions, especially CIN2+,⁹² there could be a potential role for lipids and IGFBP-3 in the persistence of cervical lesions.

We did not measure serum IGF-1, and thus we did not estimate the IGF-1 to IGFBP-3 molar ratio, which could also be used to derive associations with treatment outcomes, as used previously.³⁰ We created categories of IGFBP-3 concentrations based on the mean concentrations in controls. This is because all of our IGFBP-3 concentrations were within the normal ranges as specified by the manufacturer of the measurement kit. In addition, all serum samples were stored at recommended temperatures and later run as a batch. This storage time may have led to reductions in the concentrations of IGFBP-3 and lipids. The fact that we used non-fasting lipid concentrations may have had an impact on triglyceride concentrations. We also experienced a high loss to follow-up rate, and this could have lowered the power of our study and also hindered derivations of associations. However, this study used internationally acceptable quantification methods for lipids and IGFBP-3. We also used standard cut-off values for categorizing abnormal lipids. The presence or absence of cervical lesions was confirmed with either a Pap smear or histology, the gold standard, at both baseline and follow-up.

Conclusion

Reduced serum concentrations of IGFBP-3 and triglycerides may be associated with clearance of cervical lesions, although this finding was not statistically significant among our study population. Larger prospective studies are recommended to further understand the biological mechanisms behind lipids, IGFBP-3, other insulin-like growth factors, and the persistence or clearance of cervical lesions. Lipid management may be beneficial in the treatment of cervical lesions.

Abbreviations

AOR, adjusted odds ratio; ASCUS, atypical squamous cells of undetermined significance; CI, confidence interval; CIN, cervical intraepithelial neoplasia; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; HPV, human

papilloma virus; HSIL, high-grade squamous intraepithelial lesion; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor binding protein-3; IUD, intrauterine device; LDL, low-density lipoprotein; LSIL, low-grade squamous intraepithelial lesion; MRRH, Mbarara Regional Referral Hospital; NILM, negative for intraepithelial lesions or malignancy; Pap, Papanicolaou; SD, standard deviation; STATA, Statistical Software for Data Science; VIA, visual inspection with acetic acid.

Data Sharing Statement

All of the data that informed this article are available from the corresponding author upon reasonable request.

Ethical Considerations

We sought written informed consent from every participant before they took part in the study. We did not use participant names on any data collection tools or laboratory specimens. We did our best to delink all participants' identifiable information before and during data analysis. All participant interaction with the research team took place in a separate, quiet and comfortable room, free from any disturbances and only accessible to one participant at any single time. This study was approved by the Mbarara University of Science and Technology Research Ethics Committee (MUST-2022-396) as well as the Uganda National Council for Science and Technology (HS2395ES). We also sought administrative clearance from the Hospital Director, Mbarara Regional Referral Hospital. All cases received the standard package of care as offered at the cervical cancer clinic. Participants received their VIA, Pap smear, histology, lipid profile and IGFBP-3 results through the nurses at the clinic. This study complied with the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported in this paper, including conception of the idea, study design, execution, acquisition of data, data analysis and interpretation, in any or all of these areas; and took part in drafting, revising or critically reviewing the article. All authors gave final approval of the final version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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