RESEARCH ARTICLE

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Melatonin Receptors in Uterine Leiomyomas: An Immunohistochemical Study

Rasha Mohamed Samir Sayed[1], Ahmed A. A. Taha[2], Ahlam Wagih Mohamed[3], Shereen Mahmoud Refaie[4], Mohamed AbdelSalam Newira[5]*, Hanaa Mohammed[3,6]

Abstract

Background: Uterine leiomyomas are the most common benign tumors in women of reproductive age, often causing significant symptoms such as abnormal bleeding, pain, and infertility. Melatonin, a hormone with anti-proliferative and oncostatic properties, has been studied; however, its effects on uterine leiomyomas remain unclear. **Objective:** This study aimed to evaluate the immunohistochemical expression of melatonin receptors *MT1* and *MT2* in uterine leiomyomas compared to normal myometrium, and to correlate their expression with clinical and histopathological features. **Methods:** A case-control study was conducted on ninety cases retrieved (60 leiomyoma cases, thirty normal myometrium controls). Immunohistochemical staining was performed to assess the expression of *MT1* and *MT2* receptors. Clinical data were collected, and statistical analyses were conducted to evaluate associations between receptor expression and demographic, clinical, and histological features. **Results:** *MT1* and *MT2* were significantly overexpressed in leiomyomas compared to controls (*MT1*: 70% vs. 30%, $p < 0.0001$; *MT2*: 60% vs. 16.7%, $p < 0.0001$). A strong positive correlation was observed between *MT1* and *MT2* expression ($r = 0.6$, $p < 0.0001$). *MT1* score varied significantly with age ($p = 0.03$), tumor location ($p = 0.04$), and presenting symptoms ($p = 0.03$), while *MT2* expression was positively associated with the number of lesions ($p = 0.033$). **Conclusion:** Melatonin receptors *MT1* and *MT2* are significantly upregulated in uterine leiomyomas, suggesting a potential role in their pathogenesis. These findings support further investigation into melatonin-based therapies as adjunctive treatments for leiomyomas.

Keywords: Melatonin receptors- *MT1*- *MT2*- uterine leiomyoma- immunohistochemistry- fibroids

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Introduction

Uterine fibroids, known as leiomyomas, are benign mesenchymal tumors derived from smooth muscle and are the most common uterine neoplasm in the reproductive years [1]. These tumors impose a substantial clinical and economic burden, frequently causing chronic pelvic pain, severe abnormal vaginal bleeding, and infertility. Important determinants of symptoms are the location (sub-mucosal, intra-mural, and sub-serosal), number, and size of leiomyomas [2, 3].

Histological variants of leiomyoma include conventional type (most common), cellular leiomyoma, leiomyoma with bizarre nuclei, fumarate hydratase-deficient, mitotically active, and epithelioid leiomyoma [4]. While the exact cause of uterine leiomyomas is not known, certain factors significantly increase the risk of developing them. These include reproductive and endocrine factors like the estrogen and progesterone life cycle, early menarche, nulliparity, race, obesity, and hypertension [5].

While surgery remains a primary management option, it carries a considerable risk of gynecological complications, underscoring the urgent need for effective, non-invasive medical therapies [6]. Melatonin is a sleep hormone that is produced naturally by the pineal gland. possesses potent antioxidant, immunomodulatory, and oncostatic properties [7, 8]. Beyond its well-known role in regulating sleep, melatonin plays a critical role in human reproduction by improving ovulation, supporting embryo implantation, and protecting endometrial cells from apoptosis [9, 10].

These biological effects are primarily mediated through two high-affinity G-protein-coupled receptors: melatonin receptor 1 (*MT1*) (also called MTNR1A or Mel1a) and melatonin receptor 2 (*MT2*) (also called MTNR1B or Mel1b) [11]. Upon activation, these receptors modulate intracellular signaling pathways, such as reducing cAMP and cGMP levels, to regulate cell growth and survival [12].

*[1]Department of Pathology, Faculty of Medicine, Aswan University, Egypt. [2]Department of Obstetrics and Gynecology, Faculty of Medicine, Sohag University, Egypt. [3]Department of Human Anatomy and Embryology, Faculty of Medicine, Sohag University, Egypt. [4]Department of Biomedical Sciences, College of Medicine, King Faisal University, Alhasa, Saudi Arabia. [5]General and Bariatric Surgery, Arab Bariatric and Plastic Center, Egypt. [6]Department of Basic Medical Sciences, Medical College, Al Rayan National Colleges, Madina, Saudi Arabia. *For Correspondence: m8abdelsalam8m@yahoo.com*

Melatonin receptors have gained significant attention due to their potential role in modulating tumor development and progression. The underlying mechanisms include antioxidant activity, modulation of melatonin receptors *MT1* and *MT2*, stimulation of apoptosis, regulation of pro-survival signaling and tumor metabolism, inhibition of angiogenesis, metastasis, and induction of epigenetic alteration [13].

While *MT1* and *MT2* have been identified in both eutopic and ectopic human endometrial tissues [14] There is currently a significant gap in knowledge regarding the significance of their expression in human uterine leiomyomas. Preliminary animal studies using Eker rat models have suggested that activating these receptors can reduce cell proliferation in leiomyoma tissue [15], but clinical data in humans remain extremely limited.

We hypothesize that *MT1* and *MT2* receptors are significantly overexpressed in human uterine leiomyomas compared to normal myometrium and that this expression correlates with specific clinicopathologic features, such as tumor size, location, and symptom severity. This study aims to use immunohistochemistry (IHC) to map receptor expression in human samples, providing a foundation for evaluating melatonin receptors as potential targets for novel, targeted leiomyoma treatments.

Materials and Methods

This is a retrospective case-control study approved by the ethics committee of the Faculty of Medicine, Aswan University, IEC Ref NO: Asu./829/9/23. The cases were collected from archived material at the Pathology Department, Faculty of Medicine, Aswan University Hospitals.

Inclusion criteria

Cases of uterine leiomyoma

Cases of normal myometrium (obtained from a hysterectomy done for reasons other than leiomyoma).

Exclusion criteria

1- Leiomyoma with extensive degenerative changes

2- Cases of smooth muscle tumors of uncertain malignant potential (STUMP) or cases of leiomyosarcoma

Cases of incomplete clinicopathological data include age, complaint, location, and number of leiomyomas.

Any case with previous hormonal therapy

In cases of more than one leiomyoma, the most presentable one with average size and a known location was chosen.

Sample size calculation

For the expected prevalence of 63% (as our previous pilot study showed positive expression of both markers in twelve cases out of nineteen 12/19), the required sample size was 90 for the margin of error or absolute precision of ±10% in estimating the prevalence with 95% confidence.

Sample size calculation according to formula: here, n=Z(1 -α/2)2x p X(1- p)/d2

Z (1 -α/2)=1.96 (value of the standard normal variate corresponding to the level of significance α of 0.05)

p =Expected prevalence of *MT1* and *MT2* expression in the study population (63% or 0.63)

d =Specified precision on either side of the mean (10% or 0.1)

n= 1.96 x1.96 x 0.63 x (1-0.63)/(0.1 x0.1)= 89.5

Approximately ninety patients are needed in this study.

The sample size included Specimens of sixty cases of uterine leiomyoma and thirty cases of normal myometrium.

Histopathological examination

Formalin-fixed paraffin-embedded (FFPE) Blocks were prepared from the collected cases. To ensure patient confidentiality, names were replaced with unique ID numbers. The blocks were then serially sectioned at a thickness of four µm and stained with Hematoxylin and Eosin (H&E) for histopathological examination. This process was conducted to document the diagnosis, identify any relevant histological subtypes, and exclude cases that met the predefined exclusion criteria. The ID numbers were consistently used on both the glass slides and the corresponding datasheets.

Immunohistochemical staining

Immunohistochemical staining was performed using an automated system (Dako Omnis, Agilent). Paraffin-embedded tissues were sectioned at 4 µm thickness, mounted on two positively charged slides from each block, heat-dried, deparaffinized, and rehydrated. Antigen retrieval was conducted in a high-pH solution at 97 °C for 30 minutes. Sections were incubated with primary rabbit polyclonal antibodies against MTNR1A (*MT1*) (Rabbit polyclonal Antibody dilution 1:200, catalog No.: A13030 ABclonal China) and MTNR1B (MT2) (Rabbit polyclonal Antibody dilution 1:200, catalog No.: bs.0963R Bioss USA) for 30 minutes at room temperature. After blocking endogenous peroxidase, a secondary antibody linker and HRP polymer were applied. Antigen–antibody reactions were visualized using DAB chromogen, followed by counterstaining, dehydration, clearing, and mounting.

Positive control

Positive control slides from rat brain were included in each staining session. (for both marks).

Negative controls

Additional tissue sections were stained simultaneously, but without utilizing the main antibody.

Immunohistochemical Evaluation

Two individuals evaluated immunohistochemistry staining. Membranous/Cytoplasmic staining [16] for MTNR1A and MTNR1B was assessed using a grading system based on the immunoreactivity intensity and the proportion of stained cells. The intensity of immunoreactivity was scored as follows: (0) for no staining, (1) for weak staining, (2) for moderate staining, and (3) for strong staining. The percentage of stained cells was scored as follows: (0) for <10%, (1) for 10–29%, (2) for 30–49%, (3) for 50–74%, and (4) for ≥75%. The intensity score and the score for the percentage of positively stained cells were multiplied to arrive at the final immunoreactive score, which ranged from 0 to 12 [17]. The scoring will be categorized into (negative (0–2), mild (3–5), moderate (6–8) & strong (9–12) [18]. We used the term positive expression for stain (≥10%) and negative expression for stain (<10%,).

Slide screening and Imaging

All slides were examined using a LEICA light microscope (ICC50 W)

Pictures are captured (Axiocam ERc5s Ziess camera Zeiss)

Statistical analysis

Data was analyzed using Statistical Software package version 27 (IBM Statistical Package for the Social Sciences co(SPSS) version 27.0, SPSS Inc., Chicago, IL, USA). Descriptive analysis was performed. Qualitative variables are presented as frequencies and percentages. Quantitative variables are presented as means and standard deviations, median and range. Parametric continuous data were compared by using independent t-test for the two tested groups and One Way ANOVA test for the three or more tested groups. Nonparametric data were compared by using Mann-Whitney Test for the two tested groups and Kruskal-Wallis Test for the three or more tested groups Qualitative variables were compared by using the Fisher exact test and Chi-square test. The Spearman rank correlation analysis was performed to determine the relationships. Scatter plots were produced by SPSS version 27. p-value was considered significant if it was less than 0.05.

Results

Summary Statistics of Demographic and Clinical Data

The study included 60 (66.7%) leiomyoma cases (mean age 41.6 ± 6.8 years) and 30 (33.3%) controls. The most common symptoms were bleeding in 43 (71.6%) and infertility in 13 (21.7%) cases. Twenty-three (38.3%) of the studied cases had single leiomyoma. Most lesions were intramural 42 (70%) with a median size of 6 cm as shown in Table (1).

Summary Statistics of Histological and Immunohistochemical Data

The histopathological features of the studied leiomyomata are shown in Table 2, Figure 1, and Figure 2.

Comparison between score and expression of MT1 and MT2 in cases and control groups

There is a highly significant difference between cases and control groups in *MT1* score, *MT1* expression, *MT2* score, and *MT2* expression as the p-value (<0.0001, <0.0001, <0.0001 and <0.0001 respectively) as shown in Table 3.

Comparison between different scores of MT1 and MT2 according to demographic, clinical, and histological data as shown in Table 1

The analysis of 60 leiomyoma cases revealed that *MT1* scores significantly correlated with younger age (p=0.03), diverse tumor locations (p=0.04), and clinical symptoms including bleeding and infertility (p=0.03). No other significant associations were found for *MT1* or *MT2* scores regarding tumor size, number, or histological subtype (Table 1).

Comparison between expressions of MT1 and MT2 according to demographic, clinical and histological data

MT1 expression showed no significant associations

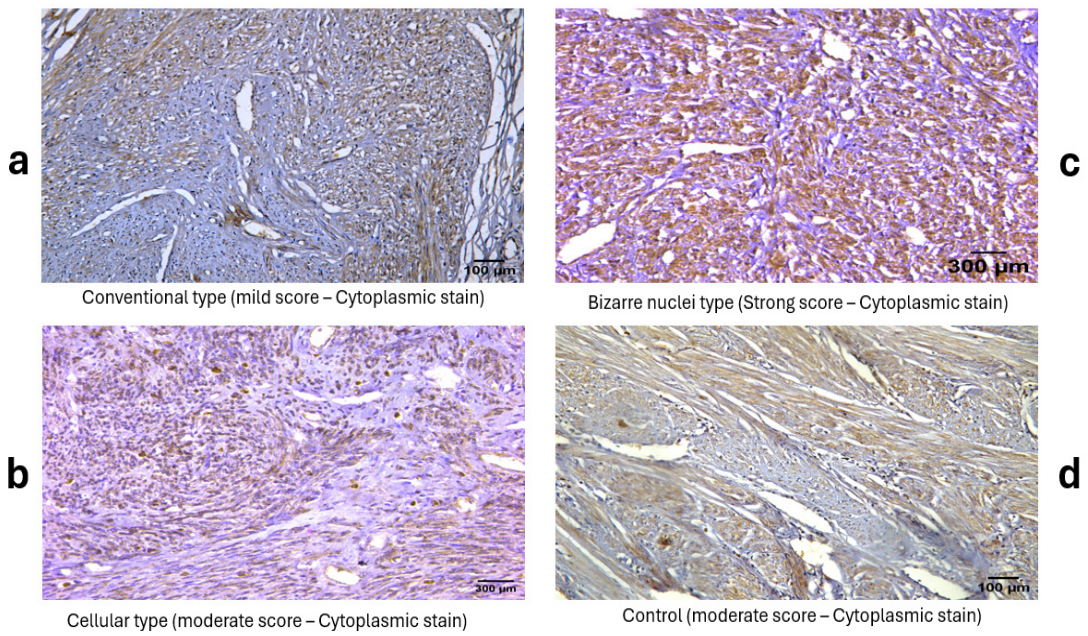

Figure 1. The IHC Score of *MT1* in Different Types of Leiomyomas and Normal Myometrium (Control)

Table 1. Comparison between Different Scores of *MT1* and *MT2* According to Demographic, Clinical, and Histological Data

Demographic, clinical and histological data	*MT1* Score				p-value	*MT2* Score				p-value
	Negative	Mild	Moderate	Strong		Negative	Mild	Moderate	Strong	
Number	6	11	16	27		11	18	15	16	
Age: Mean ±SD	46.7±5.9	44.7±6.2	41.2±6.6	39.4±6.5	0.03*	41.6±6.2	40.7±7.5	42.3±6.8	41.8±7	0.93 (NS)
Size(cm)	5.5	7	6	5	0.26 (NS)	6	6	5	6	0.45 (NS)
Median (min-max)	(3-10)	(3-15)	(3-16)	(2-15)		(3-15)	(3-16)	(2-13)	(3-15)	
Number										
Single	2	3	9	9	0.15 (NS)	6	4	7	6	0.057 (NS)
Double	1	7	4	8		0	9	3	8	
Multiple	3	1	3	10		5	5	5	2	
Location										
Sub-mucosal	0	0	2	7	0.04*	2	1	2	4	0.4 (NS)
Intra-mural	6	11	9	16		7	12	12	11	
Sub-serosal	0	0	5	4		2	5	1	1	
Complaint										
Pain	0	0	4	0	0.03*	2	2	0	0	0.37 (NS)
Bleeding	5	10	9	19		8	11	12	12	
Infertility	1	1	3	8		1	5	3	4	
Histology										
Conventional type	4	9	9	14	0.43 (NS)	9	14	6	7	0.12 (NS)
Cellular	2	0	5	8		2	3	5	5	
Bizarre nuclei	0	2	2	5		0	1	4	4	

MT1, Melatonin Receptor 1; *MT2*, Melatonin Receptor 2. SD, Standard Deviation. NS, Non-significant ($p > 0.05$). (*), Statistically significant difference ($p < 0.05$). Continuous data presented as Mean ± SD (Age) or Median (min-max) (Size). Statistical tests used: One-way ANOVA and Kruskal-Wallis tests.

Table 2. Summary Statistics of Histological and Immunohistochemical Data

Histological and Immunohistochemical data	Summary Statistics
Histology (Number = 60)	
Conventional type	36 (60%)
Cellular	15 (25%)
Bizarre nuclei	9 (15%)
MT1 Score (Number = 90)	
Negative	27 (30%)
Mild	18 (20%)
Moderate	18 (20%)
Strong	27 (30%)
MT1 Expression (Number = 90)	
Negative	27 (30%)
Positive	63 (70%)
MT2 Score (Number = 90)	
Negative	36 (40%)
Mild	23 (25.6%)
Moderate	15 (16.6%)
Strong	16 (17.8%)
MT2 Expression (Number = 90)	
Negative	36 (40%)
Positive	54 (60%)

with demographic, clinical, or histological parameters, whereas *MT2* expression was significantly correlated with the number of lesions (p=0.033) Table 4.

Correlation between MT1 and MT2 expressions and scores

There was a highly significant moderate positive correlation between *MT1* Score and *MT2* Score (p-value <0.0001) and a correlation coefficient = 0.52. There was also a highly significant strong positive correlation between *MT1* Expression and *MT2* Expression (p-value <0.0001) and correlation coefficient = 0.6 (Figure 3).

Discussion

The findings of this study provide insights into the demographic, clinical, histological, and immunohistochemical characteristics of uterine leiomyoma.

Studies have established the presence of melatonin receptors in different human tissues. Until now, studies about the effect of melatonin on the inhibition of uterine leiomyoma and mapping the expression of melatonin receptors in human myometrium and in leiomyoma are still insufficient.

To our knowledge this is the first study that aims to localize the presence of melatonin receptors, *MT1* and *MT2*, at the cellular level in normal myometrium and leiomyoma using IHC. This provides the basis for upcoming research on the regulatory function of melatonin in leiomyoma.

In 2003, Schlabritz-Loutsevitch et al. identified mRNA

Table 3. Comparison between Score and Expression of *MT1* and *MT2* in Cases and Control Groups

Immunohistochemical expression	Total 90	Control 30	Cases 60	p-value
MT1 Score				
Negative	27	21	6	
Mild	18	7	11	<0.0001*
Moderate	18	2	16	
Strong	27	0	27	
MT1 Expression				
Negative	27	21	6	<0.0001*
Positive	63	9	54	
MT2 Score				
Negative	36	25	11	
Mild	23	5	18	<0.0001*
Moderate	15	0	15	
Strong	16	0	16	
MT2 Expression				
Negative	36	25	11	<0.0001*
Positive	54	5	49	

for both *MT1* and *MT2* melatonin receptor isoforms in human myometrial biopsies from both pregnant and nonpregnant women, using RT-PCR and in situ hybridization. They also showed specific high-affinity binding of iodomelatonin to these tissues. Importantly, primary cultures of myometrial cells responded differently to melatonin's cAMP signaling depending on the reproductive state. These findings suggest that melatonin can modulate human myometrial function, potentially paving the way for new therapeutic approaches [19].

Demographic and Clinical Characteristics

The study population consisted of ninety women, with sixty cases of uterine leiomyoma and thirty controls. The mean age of cases (41.6 ± 6.8 years) aligns with the typical age range for uterine leiomyoma diagnosis, as these tumors are mostly diagnosed in women of reproductive age [20]. The primary complaints among cases included abnormal uterine bleeding (71.6%), infertility (21.7%), and pelvic pain, which are consistent with the well-documented symptomatology of uterine leiomyoma [21]. The distribution of leiomyoma locations (70% intramural, 15% sub-mucosal, and 15% sub-serosal) and sizes (median 6 cm, range 2–16 cm) further reflects the heterogeneity of these tumors, which is a known challenge in their management.

Histological and Immunohistochemical Findings

Histologically, most leiomyomas were classified as Conventional type (60%), with smaller proportions being cellular (25%) or Leiomyoma with bizarre nuclei (15%). These findings are consistent with the typical histopathological spectrum of uterine leiomyoma [22].

Table 4. Comparison between Expressions of *MT1* and *MT2* According to Demographic, Clinical and Histological Data

Demographic, clinical and histological data	Total	*MT1* Expression		p-value	*MT2* Expression		p-value
		Negative	Positive		Negative	Positive	
	60	6	54	0.052 (NS)	11	49	0.97 (NS)
Age: Mean ±SD		46.7±5.9	41±6.7		41.6±6.2	41.6±7	
Size (cm)		5.5	6	0.99 (NS)	6	6	0.69 (NS)
Median (min-max)		(3-10)	(2-16)		(3-15)	(2-16)	
Number							
Single	23	2	21	0.43 (NS)	6	17	0.033*
Double	20	1	19		0	20	
Multiple	17	3	14		5	12	
Location							
Sub-mucosal	9	0	9	0.24 (NS)	2	7	0.88 (NS)
Intra-mural	42	6	36		7	35	
Sub-serosal	9	0	9		2	7	
Complaint							
Pain	4	0	4	0.72 (NS)	2	2	0.16 (NS)
Bleeding	43	5	38		8	35	
Infertility	13	1	12		1	12	
Histology							
Conventional type	36	4	32	0.54 (NS)	9	27	0.19 (NS)
Cellular	15	2	13		2	13	
Bizarre nuclei	9	0	9		0	9	

MT1, Melatonin Receptor 1; *MT2*, Melatonin Receptor 2; Positive Expression, Staining ≥ 10%; Negative Expression: Staining < 10%; SD: Standard Deviation; NS: Non-significant (p > 0.05); (*) Statistically significant (p < 0.05); Statistical comparisons were performed using independent t-tests (parametric) and Mann-Whitney tests (non-parametric)

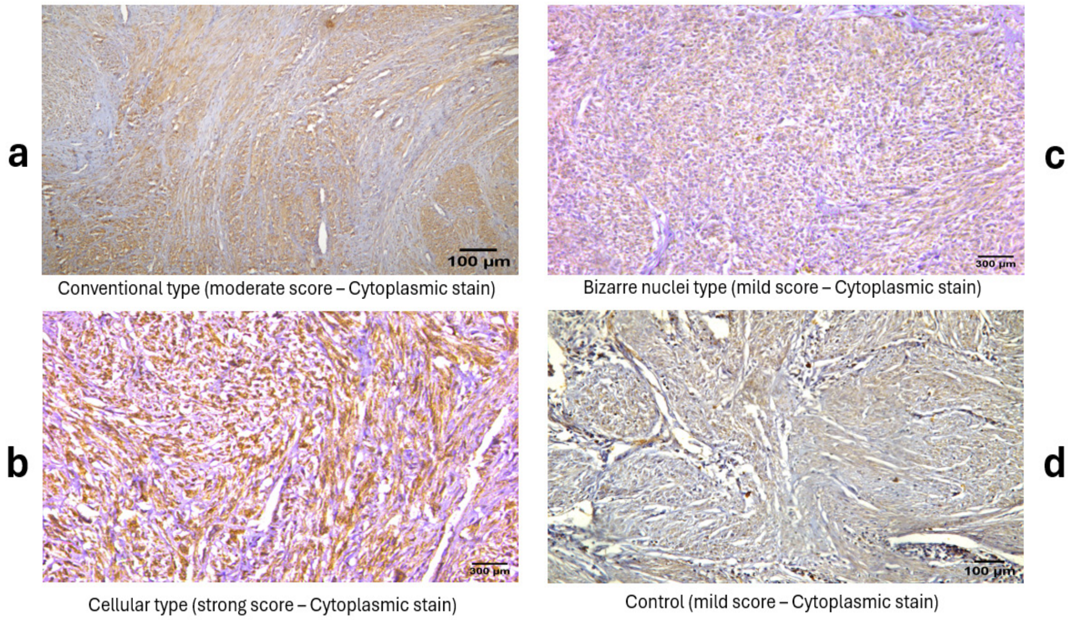

Figure 2. The IHC score of *MT2* in Different Types of Leiomyomas and Normal Myometrium (Control)

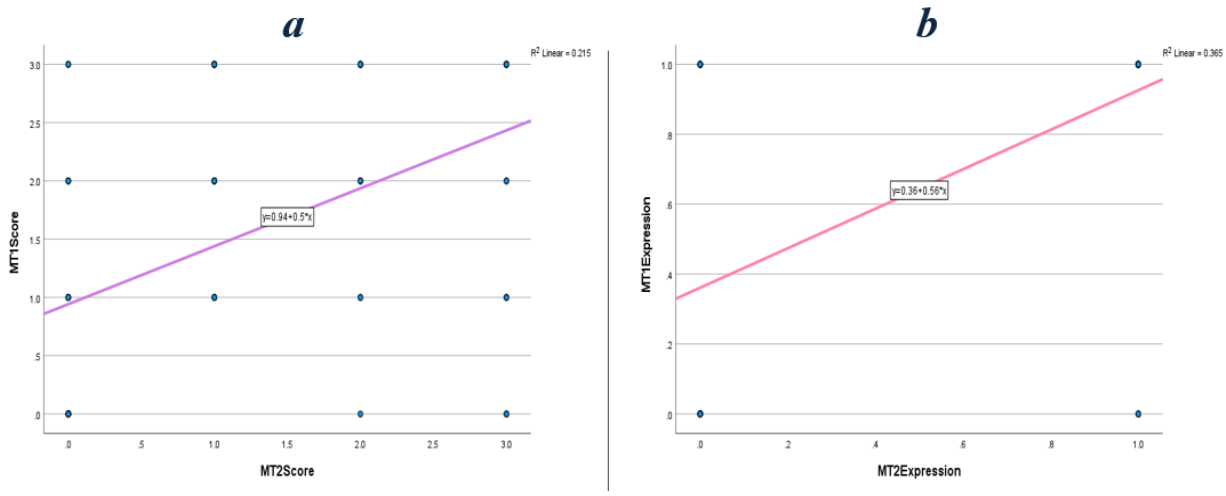

Figure 3. Graph (a) shows a highly significant, moderate positive correlation between MT1 and MT2 scores (correlation coefficient = 0.52). Graph (b) shows a highly significant, strong positive correlation between MT1 and MT2 expression (correlation coefficient = 0.6).

(Figure 1 and Figure 2).

The immunohistochemical analysis revealed that *MT1* and *MT2* were significantly overexpressed in leiomyoma cases compared to controls. Specifically, 70% of cases were positive for *MT1* expression and 60% for *MT2* expression. This suggests that both markers may play a role in the development or progression of uterine leiomyoma.

A comparative study by Sokolov et al., over 80 women (60 suffering from leiomyoma and 20 controls), found that the level of melatonin in the blood of women of reproductive age suffering from uterine leiomyoma significantly decreases (by 27.6 %) compared to healthy women of the same age group [12]. Considering the two previous paragraphs, women suffering from leiomyoma show overexpression of *MT1* and *MT2* receptors (our study) as a compensatory response to the decreased plasma levels of melatonin [12] to restore this lost regulatory signal.

The strong positive correlation between *MT1* and *MT2* expression ($r = 0.6$, $p < 0.0001$) and their scores ($r = 0.52$, $p < 0.0001$) suggests a possible synergistic or interrelated role in the pathophysiology of these tumors. This correlation aligns with previous studies that have implicated *MT1* and *MT2* in cellular proliferation, apoptosis regulation, and tumorigenesis in various tissues [23]. Lin et al. investigated melatonin's impact on uterine leiomyoma growth using both an Eker rat-derived cell line (ELT3) and primary human uterine smooth muscle cells (UtSMC), along with the underlying molecular mechanisms [15]. Their research revealed that melatonin significantly reduced the growth of ELT3 cells, both in vitro and in vivo through xenograft and orthotopic uterine tumor mouse models. Notably, melatonin exhibited a selective effect: it protected normal UtSMC cells by arresting their cell cycle but simultaneously triggered programmed cell death in ELT3 leiomyoma cells. These results collectively indicate melatonin's potential to suppress uterine leiomyoma growth, with the *MT1* receptor being more influential than *MT2* in mediating this signaling suppression [15].

It is to be noted that Lin et al. 's work focused on the action of melatonin over Eker rat-derived uterine leiomyoma ELT3 cell line, while we assessed the expression of *MT1* and *MT2* receptors in human uterine leiomyoma in contrast to human uterine smooth muscle tissue. In addition, melatonin has a circadian nature, which means that the Correct timing of melatonin assessment is crucial, which is not the case when assessing *MT1* and *MT2* expression.

A meta-analysis concluded that oral melatonin, when used by itself or alongside chemotherapy, significantly benefited cancer patients. It improved survival, enhanced treatment response, and slowed disease progression. Furthermore, melatonin lessened the toxic side effects of several chemotherapy drugs. These advantages were observed consistently across several types of solid cancers, showing melatonin's widespread impact.

Association with Demographic, Clinical, and Histological Features

The current study identified significant associations between *MT1* score and specific clinical and demographic factors. For instance, *MT1* scores varied significantly with age ($p = 0.03$), lesion location ($p = 0.04$), and patient complaints ($p = 0.03$). These findings suggest that *MT1* may be influenced by hormonal or microenvironmental factors that vary with age and tumor location. The association with patient complaints, particularly bleeding and pain, further highlights the potential role of *MT1* in symptom manifestation.

In contrast, *MT2* expression showed a significant association only with the number of lesions ($p = 0.033$), suggesting that *MT2* may be more involved in the multifocality or growth patterns of leiomyoma rather than their clinical presentation. The lack of significant associations between *MT2* and other demographic or clinical factors indicates that its role may be more specific to tumor biology rather than patient-specific variables.

Limitations

This study is limited by its reliance on immunohistochemistry, which, while informative, does not provide insights into the functional activity of melatonin receptors. Additionally, the relatively small sample size may limit the generalizability of the findings.

In conclusion, our study demonstrates the presence of melatonin receptors, *MT1* and *MT2*, throughout the leiomyoma and in the normal myometrium.

Melatonin receptors (*MT1* and *MT2*) may represent potential targets for the development of novel therapies. From this perspective, melatonin could be considered a promising adjunctive agent for the management of uterine leiomyoma, though further clinical trials are necessary to evaluate its efficacy and safety in a clinical setting.

Future directions

Additional studies on women experiencing low levels of melatonin and the risk of developing fibroid are necessary.

Future clinical trials should explore the efficacy of melatonin supplementation in women with symptomatic leiomyoma, with attention to optimal dosing and timing to mimic endogenous circadian rhythms.

Author Contribution Statement

All authors contributed to the study design, data collection, and manuscript drafting. Rasha Mohamed Samir Sayed: Conceptualization, methodology, investigation (lead), data curation, writing – original draft preparation, and supervision. M. AbdelSalam N: Formal analysis (statistical analysis), writing – original draft preparation, and visualization. Ahmed A. A. Taha: Investigation (immunohistochemical evaluation), supervision, and writing – review and editing. Ahlam Wagih Mohamed: Methodology validation and resources. Shereen Mahmoud Refaie: Resources and manuscript formatting. Hanaa Mohammed: Formal analysis (statistical analysis) and software. All authors have read and agreed to the published version of the manuscript.

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Thesis status

This manuscript is not a part of a thesis study.

Scientific Body Approval

The research protocol was approved by the Institutional Review Board (IRB) of the Faculty of Medicine, Aswan University. For this retrospective analysis of de-identified histopathological samples from the Department of Pathology, the requirement for informed consent was waived in accordance with institutional guidelines.

Ethical Approval

The study was approved by the Ethics Committee of the Faculty of Medicine, Aswan University IEC (Ref NO: Asw.U./829/9/23).

Availability of data

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Registration

This study was not a clinical trial and thus was not registered in a clinical trial database.

Conflict of Interest

The authors declare no conflicts of interest.

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