Detection of β-Catenin Expression in Endometrial Tumors among Sudanese patients using Immunohistochemistry

الكشف عن ظهور البيتاكاتينين في أورام بطانة الرحم بين المرضى السودانيين باستخدام كيمياء ومناعة الأنسجة

A dissertation submitted for partial fulfilment for the requirements of master degree in medical laboratory science (Histopathology and Cytology)

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قال تعالى:

ولقد خلقنا الإنسان من نسلة من طين (12) ثم جعلناه نطفة في قارٍ مكين (13) ثم خلقنا النطفة علما خلقنا العلامة صخراَ خلقنا المضنة عظاماً فكسرنا العظام لحمنا ثم أنشأنا خلقا آخر فنمارك الله أحسن الخالقين (14)

صدق الله العظيم
سورة المؤمنون من الآية (12-14)
Dedication

To my mother,

A strong and gentle soul who taught me to trust in Allah, believe in myself to reach the stars and chase my dreams.

To my father,

My hero, who giving me the strength and courage to make it through.

To my sisters, little brother,

Who always beside me for better and worse.

To my best friends,

Thank you for being in my life.
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Abstract

This is a hospital based analytical retrospective case control study was conducted at Ribat University Hospital, Soba University Hospital, Omdurman Military Hospital (Khartoum state) and Sudan university of science and technology- college of medical laboratory science, during the period from June to October 2016. The study was aimed to detect beta-catenin expression in endometrial tumors, using immunohistochemistry.

Forty paraffin block samples were collected from patients previously diagnosed as endometrial tumors, 20 (50%) of them were malignant and 20 (50%) were benign. The histopathological diagnosis of study population includes 8 (40%) endometrioid adenocarcinoma, 6 (30%) papillary carcinoma, 5 (25%) squamous cell carcinoma, 1 (5%) malignant mixed mullerian tumor, 4 (20%) atypical hyperplasia, 16 (80%) non atypical hyperplasia.

The age of patients ranged between 25 to 85 years with the mean age of 56.4 ± 14.9 years. The present study revealed that most patients 22 (55%) were above 60 years and the remaining 18 (45%) were below 60 years.

The paraffin blocks were cut by rotary microtome, then stained by immunohistochemical method (new indirect technique). The data obtained was analysed using SPSS program version 20. Mean, standard deviation, frequencies and Chi square test were calculated.

Beta-catenin expression was found positive in 13 (65%) of malignant samples and negative in the remaining 7 (35%). While all benign samples were positive with a significant association between β-catenin expression and endometrial tumors (P. value = 0.004).

The study concluded that there is a significant relationship between β-catenin expression and endometrial tumors.
المستخلص

أجريت هذه الدراسة المستشفيّة التحليلية الإسترجاعية حالة وحالة ضابطة في مستشفى الرباط الجامعي، مستشفى سويا الجامعي، المستشفى العسكري - أمدرمان (ولاية الخرطوم) وجامعة السودان للعلوم والتكنولوجيا، كلية علوم المختبرات الطبية، في الفترة من يونيو إلى أكتوبر 2016، هدفت الدراسة للكشف

ظهور البيتاكتينين في أورام بطانة الرحم باستخدام كيمياء ومناعة الأنسجة.

جمع أربعون قلبة مهماً من عينات مرضى كاثومشخّسين مسبقاً على أنهم مصابين بأورام بطنية الرحم، 20% (50) أورام بطنية رحم خبيثة و 20% (50) أورام بطنية رحم حميدة. كان تشخيص المرضى تحت الدراسة يتضمن علاج هادئ لسالة بطنية غدي شبه بطنية الرحم 8 (40%) عينة، وسرطان حليمي 6% (30%) عينة، وسرطان الخلايا الحشرفية 5% (25%) عينة، أورام مولر الخبيثة المخلتة 1% (5%).

فقط اللدود البيرناميتي 4% (20%) عينة، فرط التنسيج النمطي 16% (80%) عينة.

تراوحت أعمار المرضى بين 45 - 55 سنة بمتوازنة عمر 42.9 ± 56.4 أظهرت الدراسة أن معظم المرضى (22% (55%)) مريضاً كانت أعمارهم فوق 60 سنة و (18% (45%)) مريضاً كانت أعمارهم دون 60 سنة.

قُطرت القوالب الشمعية باستخدام المشراح الدوار، ثم صُبّت بواسطة كيمياء ومناعة الأنسجة (الطريقة الجديدة غير المباشرة). تم تحليل البيانات باستخدام برنامج الحزم الإحصائي للأعمال الاجتماعية، النسخة 20 لتحليل البيانات حسب متوسط التكرار والانحراف المعياري وقيم اختبار معياري.

أظهرت الدراسة أن البيتاكتينين كان موجب الظهور في 13% (65%) عينة من أورام بطنية الرحم الخبيثة وسالب الظهور في 7% (35%) المتبقي. بينما لكل عينات أورام بطنية الرحم الحميدة كانت موجبة الظهور مع وجود علاقة ذات دلالة إحصائية بين إفراز البيتاكتينين وأورام بطنية الرحم (P. value = 0.004).

خلصت الدراسة إلى أنه توجد علاقة ذات دلالة إحصائية بين إفراز البيتاكتينين وأورام بطنية الرحم.
## List of contents

<table>
<thead>
<tr>
<th>Contents</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>الادبية</td>
<td>I</td>
</tr>
<tr>
<td>Dedication</td>
<td>II</td>
</tr>
<tr>
<td>Acknowledgement</td>
<td>III</td>
</tr>
<tr>
<td>Abstract (English)</td>
<td>IV</td>
</tr>
<tr>
<td>Abstract (Arabic)</td>
<td>V</td>
</tr>
<tr>
<td>List of contents</td>
<td>VI</td>
</tr>
<tr>
<td>List of figures</td>
<td>VIII</td>
</tr>
<tr>
<td>List of tables</td>
<td>IX</td>
</tr>
<tr>
<td>List of microphotographs</td>
<td>X</td>
</tr>
</tbody>
</table>

### Chapter One – Introduction

1.1 Introduction 1

1.2 Objectives 3

### Chapter Two – Literature Review

2.1 Scientific background 4

2.2 Structure of the endometrium 4

2.3.1 Disorders of endometrium (benign) 5

2.3.2 Disorders of endometrium (malignant) 7

2.4 Epidemiology of endometrial cancer 8

2.5 Risk factors of endometrial cancer 9

2.6 Diagnosis of endometrial cancer 12

2.7 Treatment of endometrial cancer 14

2.8 β-catenin and its relation with endometrial cancer 15

### Chapter Three – Materials and Methods

3.1 Materials 16
3.2 Methods  
3.2.1 Study design  16  
3.2.2 Study population  16  
3.2.3 Study area  16  
3.2.4 Sample processing  16  
3.2.5 Immunohistochemical staining  16  
3.2.6 Result interpretation  17  
3.2.7 Data analysis  17  
3.2.8 Ethical consideration  17

**Chapter Four – Results**

4.1 Results  18

**Chapter Five – Discussion**

5.1 Discussion  26

**Chapter Six– Conclusion and Recommendations**

6.1 Conclusion  28  
6.2 Recommendations  29

**References**  30

**Appendices**  34
**List of figures**

<table>
<thead>
<tr>
<th>Figure No.</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure (4.1)</td>
<td>Frequency of age group among the study Population</td>
<td>19</td>
</tr>
</tbody>
</table>
### List of tables

<table>
<thead>
<tr>
<th>Table No.</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table (4.1)</td>
<td>Distribution of histopathological diagnosis among the study population</td>
<td>20</td>
</tr>
<tr>
<td>Table (4.2)</td>
<td>Frequency of malignant tumor grade</td>
<td>21</td>
</tr>
<tr>
<td>Table (4.3)</td>
<td>Frequency of immunohistochemical result of β-catenin in endometrial tumor</td>
<td>22</td>
</tr>
<tr>
<td>Table (4.4)</td>
<td>Relation between histopathological diagnosis and β-catenin expression</td>
<td>23</td>
</tr>
</tbody>
</table>
### List of microphotographs

<table>
<thead>
<tr>
<th>Microphotograph No.</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microphotograph (4.1)</td>
<td>Non-keratinized squamous cell carcinoma of endometrium showed positive membranous expression of β-catenin (100X)</td>
<td>24</td>
</tr>
<tr>
<td>Microphotograph (4.2)</td>
<td>Papillary adenocarcinoma of endometrium showed negative expression of β-catenin (100X)</td>
<td>25</td>
</tr>
</tbody>
</table>
Chapter One
Introduction
Chapter One

Introduction

1.1 Introduction:

Endometrial cancer is a primary malignant lesion arising in the endometrium and has the potential to invade the myometrium and to spread to distant sites (Ahmed and Eman, 2014).

Two different clinicopathologic subtypes of endometrial cancer has been recognized: type I and type II. Type I (estrogen-related) includes endometrioid adenocarcinomas that represent 80-90% of endometrial carcinoma arising from atypical endometrial hyperplasia. Type II (non-estrogen-related) represent the remaining 10-20% including papillary serous, clear cell endometrial carcinoma and other histological variants. Non-endometrioid carcinoma are mostly poorly differentiated and aggressive, with a 50% recurrence rate and mortality rate of 50–60% of patients with stage I–II disease (Zhongfu, et al. 2016).

Endometrial cancer is the most common gynecologic malignancy in women worldwide, with increasing incidence in socio-economic developed countries (Silvana, et al. 2015).

In Sudanese population, uterine cancer is the ninth common cancer in women and the fourth most common malignant tumor of the female genital tract after carcinomas of breast, cervix, and ovary (Mohammed, et al. 2014).

Several risk factors for the development of endometrial cancer have been identified. These include: nulliparity, late menopause, obesity, diabetes mellitus, unopposed estrogen therapy, tamoxifen therapy, atypical endometrial hyperplasia, hereditary nonpolyposis colorectal cancer (HNPCC) syndrome, polycystic ovary syndrome and functioning ovarian tumors. Other medical conditions such as hypertension, hypothyroidism have been associated with endometrial cancer (Berek, 2007).
Methods of endometrial cancer diagnosis include endometrial biopsy, transvaginal ultrasonography, sonohysterography, hysteroscopy, computed tomography (CT) and magnetic resonance imaging (MRI) (Karsten, et al. 2004).

Surgical resection remains the standard treatment for endometrial cancer, either by total hysterectomy or bilateral salpingo-oophorectomy. Other treatment options include: adjuvant radiotherapy, adjuvant chemotherapy, hormonal therapy and targeted therapy (Iglesias and Diane. 2012).

β-catenin is a component of the cadherin-catenin complex that mediate cell-cell adhesion, and plays an important role in signal transduction. β-catenin mutation results in the stabilization of proteins that are degradation resistant, thus resulting in cytoplasmic and nuclear β-catenin accumulation and constitutive target gene activity. Several studies have analysed endometrial cancer samples by immunohistochemistry, showing that β-catenin expression is significantly more common in endometrioid lesions (31% to 47%) compared to non-endometrioid tumors (0% to 3%). In another report, β-catenin expression was more frequent in endometrial hyperplasia than in endometrial carcinoma samples, suggesting a β-catenin role in the early development of endometrial cancer (Tsuyoshi, et al. 2010).
1.2 Objectives:

1.2.1 General objective:
To study the expression of beta-catenin in endometrial tumors among Sudanese women using immunohistochemistry.

1.2.2 Specific objectives:
To detect beta-catenin expression in endometrial tumors using immunohistochemistry and its correlation with histological diagnosis.
Chapter Two
Literture Review
Chapter Two
Literature Review

2.1 Scientific background:
Endometrial cancer is a disease occur primarily in postmenopausal women in their sixth or seventh decades of lives and is increasingly virulent with advancing age (Berek, 2007).
Endometrial cancer is the most common gynecological malignancy among women around the world. It is one of the most serious health problem and a major cause of morbidity and mortality for women worldwide, with almost 200,000 cases diagnosed every year (Zhongfu, et al. 2016).

2.2 Structure of endometrium:
The endometrial cavity is triangular in shape and represents the mucosal surface of the uterine corpus. It undergoes cyclic structural and functional change during the reproductive years, with regular shedding of the superficial endometrium and regeneration from the basal layer (Berek, 2007).
The surface of the endometrium is covered by a single layer of low columnar cells (capsule) which rests on inconspicuous membrane of double layer commonly called the basement membrane or membrana propria (Baggish, et al. 2007).
The endometrium is subdivided into the basal layer (stratum basalis) is adjacent to the myometrium and consist of tubular glands, occasionally branching, lined by simple to pseudostratified epithelium in a more basophilic, compact stroma. The stromal cells also appear more prominent as they are composed of largely spindled nuclei and have indistinct cytoplasm. The remaining endometrium is the functional zone (stratum functionalis), which is further subdivided into the superficial compact layer (stratum compactum) and deeper spongy layer (stratum spongiosum). The endometrial glandular cells are of three types: the secretory cell, the ciliated cell and the clear cell (Robboy, et al. 2009).
2.3 Disorders of endometrium:

2.3.1 Benign disorders:

2.3.1.1 Endometrial inflammation (Endometritis):

The endometrium is relatively resistant to infections. Acute reactions are virtually limited to bacterial infections that arise after parturition or miscarriage, retained products of conception are the usual predisposing influence. Chronic endometritis occur in the following settings: in association with chronic gonorrhreal pelvic disease, tuberculosis either from miliary spread or more commonly from drainage of tuberculous salpingitis, in postpartal or postabortal endometrial cavities usually caused by retained gestational tissue, in patients with intrauterine contraceptive devices (IUDs) and spontaneously without apparent cause in 15% of patients (Kumar, et al. 2003).

2.3.1.2 Adenomyosis:

Adenomyosis refers to the growth of the basal layer of the endometrium down into the myometrium. Nets of endometrial stroma or glands, or both, are found well down in myometrium between the muscle bundles. The uterine wall often becomes thickened, owing to the presence of endometrial tissue and reactive hypertrophy of the myometrium. Cyclic bleeding into penetrating nests, producing hemosiderins pigmentation is extremely unusual because of the stratum basalis of the endometrium from which penetration arise, is non-functional (Kumar, et al. 2003).

2.3.1.3 Endometriosis:

Endometriosis is defined as the presence of endometrial tissue (glands and stroma) outside the uterus. The most frequent site of implantation are the pelvic viscera and the peritoneum, uncommonly the lymph nodes, lungs, and even heart or bone are involved. Endometriosis varies in appearance from a few minimal lesions on otherwise intact pelvic organs to massive ovarian endometrioti cysts
that distort tubo-ovarian anatomy and extensive adhesions often involving bowel, bladder, and ureter. Endometriosis is predominantly found in women of reproductive age but has been reported in adolescents and in postmenopausal women receiving hormonal replacement and often is associated with pelvic pain and infertility (Berek, 2007).

2.3.1.4 Endometrial polyp:

Endometrial polyps are common and may present in variety of ways, including abnormal vaginal bleeding and as an incidental abnormality identified either when a cervical smear is taken or during curettage. Endometrial polyps are most commonly benign and composed of endometrial glands and stroma with a fibrovascular core, many are related to minor endocrine abnormalities such as anovulatory cycles. However, invasive carcinoma may present as a polyp and it is therefore important that all endometrial polyps be submitted for histological examination (Levison, et al. 2008).

2.3.1.5 Endometrial hyperplasia:

Endometrial hyperplasia is defined as abnormal proliferation of endometrial gland that range from mild proliferation to endometrial cancer. The World Health Organization (WHO) classification of endometrial hyperplasia includes hyperplasia without atypia (simple or complex) and hyperplasia with atypia (simple or complex) based on the degree of architectural crowding and complexity and the presence of cytologic atypia (Kimberly, et al. 2012). Simple hyperplasia shows the lowest risk of cancer progression and most cases (80%) of this naturally regress. Endometrial hyperplasia with cytological atypia is considered as direct precancerous lesions and may carry a higher risk of progression to carcinoma, all risk factors of endometrial carcinoma could be related to endometrial hyperplasia (Vishal, et al. 2016).
2.3.2 Malignant disorders:

2.3.2.1 Endometrioid adenocarcinoma:
The endometrioid type of adenocarcinoma account for about 80% of endometrial carcinoma. These tumors are composed of gland that resemble normal endometrial glands, they have columnar cells with basally oriented nuclei, little or no intracytoplasmic mucin, and smooth intraluminal surfaces. As tumors become less differentiated, they contain more solid areas, less glandular formation, and more cytologic atypia. The well differentiated lesions may be difficult to separate from atypical hyperplasia. About 15% to 25% of endometrioid carcinoma have areas of squamous differentiation. A villoglandular configuration is present in about 2% of endometrioid carcinomas. Secretary carcinoma is a rare variant of endometrioid carcinomas that accounts for about 1% of cases (Berek, 2007).

2.3.2.2. Mucinous carcinoma:
About 5% of endometrial carcinomas have a predominant mucinous pattern in which more than one half of tumor is composed of cells with intracytoplasmic mucin. Most of these tumors have a well differentiated glandular architecture, their behavior is similar to that of common endometrioid carcinomas and the prognosis is good. It is important to recognize mucinous carcinomas of the endometrium as an entity and to differentiate it from endocervical adenocarcinoma (Berek, 2007).

2.3.2.3 Papillary serous carcinoma:
Serous carcinomas typically arise in the atrophic uteri of postmenopausal women, in an older age group than women with endometrioid carcinomas. These tumors are not hormone dependent, typically have a fine papillary pattern with hierarchical branching papillae. Serous carcinomas are often associated with lymph vascular space and deep myometrial invasion, even when these
tumors appears without myometrial invasion they behave more aggressively than endometrioid carcinomas (David, et al. 2006).

2.3.2.4 Clear cell carcinoma:

Clear cell carcinoma account for less than 5% of all endometrial carcinomas. The cells have highly atypical nuclei and abundant clear or eosinophilic cytoplasm. Clear cell carcinoma characteristically occurs in older women and is very aggressive type of endometrial cancer (Berek, 2007).

2.3.2.5 Squamous carcinoma:

Squamous carcinoma of the endometrium is rare. Some tumors are pure, but some have few glands. To establish primary origin within the endometrium, there must be no connection with or spread from cervical squamous epithelium. Squamous carcinoma often is associated with cervical stenosis, chronic inflammation, pyometra at the time of diagnosis (Berek, 2007).

2.3.2.6 Malignant mixed mullerian tumors:

Carcinosarcomas or malignant mixed mullerian tumors (MMMTs) have features of both epithelial and mesenchymal neoplasm. The behaviour of carcinosarcoma is very aggressive but resemble that of high grade endometrioid type of endometrial carcinoma (David, et al. 2006).

2.4 Epidemiology:

Endometrial cancer is the most common gynecologic malignancy worldwide and the fourth most common cancer in women in the United States. However, in developing countries, it is the second most common gynecologic malignancy with an incidence of 5.9 per 100,000 women. The overall annual mortality rate has increased more than 100% during the past two decades (Edward, 2009). Approximately 8590 deaths from this disease are estimated to occur in the United States in 2014 with increasing incidence in white women comparing to
black women, yet mortality rate are higher in the black. Endometrial carcinoma is more common during the 6th and 7th decades of life, with the mean age of patients being 65 years (Silvana, et al. 2015).

In Sudan, there are two sources of data available, the Radiation Isotope Center in Khartoum (RICK) and National Cancer Institute of the University of Gezira at Wadmadani (NCI-UG). Among 13933 new cancer cases that diagnosed and treated during the period 2000 - 2006, uterine cancer ranked the fourth among most commonly diagnosed cancer of female genital tract and the ninth among all cancers diagnosed (Mohammed, et al. 2014).

2.5 Risk factors:

2.5.1 Nulliparity:
Nulliparity is associated with an increased risk of endometrial cancer. Parous women are 20% to 40% less likely than nulliparous women to develop endometrial cancer. Elevated progesterone levels during pregnancy could inhibit estrogen-driven endometrial cell proliferation and promote differentiation and apoptosis of endometrial cells. Certain infertility conditions, such as anovulatory disorders, that lead to nulliparity could also contribute to higher endometrial cancer risks among nulliparous women (Sara, et al. 2013).

2.5.2 Early menarche:
Early menarche, defined as less than 11 or 12 years of age at onset of menstrual cycle, has been link to increased risk of endometrial cancer in several studies. The effect of early menarche on endometrial cancer is greater in younger women (Holman and Karen. 2012).

2.5.3 Late menopause:
Natural menopause occurring after age of 52 years increases the risk for endometrial cancer 2.4 times compared with women who experienced
menopause before 49 years of age, probably as a result prolonged exposure of the uterus to progesterone-deficient menstrual cycle (Berek, 2007).

2.5.4 Obesity:

Among the most obesity-driven malignancies are the gynecologic cancers, particularly endometrial cancer. Approximately 50% of all new diagnoses of endometrial cancer are attributable to obesity alone. Obese women have 2.4–4.5 times the risk of being diagnosed with endometrial cancer compared with normal weight women (Anna, et al. 2016).

2.5.5 Hormone replacement therapy:

There is strong evidence that estrogen-only hormone replacement therapy (HRT) increases the risk of endometrial cancer. The risk of developing the disease appears to be proportional to the duration of estrogen therapy, after 10 years of estrogen replacement therapy (ERT), the risk is elevated about 10 fold compared to that in a lifetime nonuser. However, unopposed oral estrogens may have a rapid effect on the endometrium and have been reported to produce precancerous endometrial lesions such as endometrial hyperplasia in only a few months. The progression of such lesions to cancer may take place in only a few years (David, et al. 2006).

2.5.6 Diabetes mellitus:

Diabetes mellitus have positive relationship with endometrial cancer, women with diabetes mellitus are at risk of developing endometrial cancer 2–3 times more than normal women. Some studies found that the increased risk associated with type 2 diabetes is not restricted to obese or overweight women (Holman and Karen. 2012).
2.5.7 Hypertension:

High blood pressure is another condition long known to be associated with endometrial cancer. Hypertension increase the risk of developing endometrial cancer by 2-4 folds (Karsten, et al. 2004).

2.5.8 Lynch syndrome:

Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer (HNPCC) syndrome, an autosomal-dominant inherited cancer susceptibility syndrome, accounts for the majority of inherited endometrial cancers and is characterized by an increased risk for colorectal cancer and endometrial cancer. For women with Lynch syndrome, the lifetime risk of endometrial cancer is estimated to be between 40% to 60% (Larissa, et al. 2013).

2.5.9 Tamoxifen therapy:

Tamoxifen is a selective estrogen receptor modulator (SERM) act as antiestrogen in breast tissues and used for treatment of breast cancer patients. Since the drug has estrogen effect in the endometrial tissue, tamoxifen therapy is associated with increased risk for development of endometrial cancer. The risk of developing cancer increase with long duration and higher dose of therapy (Holman and Karen. 2012).

2.5.10 Estrogen-producing tumor:

Tumor with estrogen production, such as ovarian tumor is known to be associated with endometrial cancer. 6-10% of patients with estrogen-producing tumors will develop endometrial cancer in their lifetime (Holman and Karen. 2012).

2.5.11 Polycystic ovary syndrome:

Women with polycystic ovary syndrome (POCS) are at risk of developing endometrial cancer four times more than normal women. Several studies reports
that up to 30% premenopausal endometrial cancer patients also having POCS assuming that elevated levels of endogenous estrogen in POCS patients led to endometrial cancer (Holman and Karen. 2012).

2.6 Diagnosis of endometrial cancer:

2.6.1 Ultrasonography:
Endovaginal and transabdominal ultrasonography of the uterus may be used for screening and early detection of endometrial cancer. Ultrasonography reveal the structural abnormalities and thickness of the endometrium, if the thickness was less than or equal to 4 mm, endometrial sampling is not required. When endometrium con not be evaluated by ultrasonography, further evaluation is necessary (Edward, et al. 2009).

2.6.2 Sonohysterography:
Saline infusion sonography (also known as sonohysterography) is another method for evaluation of endometrial abnormalities. In the procedure, sterile saline is instilled into the uterine cavity before ultrasound evaluation to allow for more precise visualization of the endometrial structures (Edward, et al. 2009). Sonohysterography can be used to differentiate between different disorders of the endometrium, including endometrial cancer, endometrial hyperplasia, fibroids, endometriosis, myoma or tamoxifen induced endometrial thickness (Karsten, et al. 2004).

2.6.5 Magnetic resonance imaging:
Magnetic resonance imaging (MRI) is considered the most accurate and specific imaging technique, is an important modality in the diagnosis and assessment of endometrial cancer (Silvana, et al. 2015).

2.6.4 Computed tomography:
Computed tomography (CTs) is another imaging technique for diagnosis and assessment of endometrial cancer patients, is used mainly for assessment of patients with advanced stages of disease. CT is less sensitive and less specific than MRI (Silvana, et al. 2015).

2.6.5 Hysteroscopy:

Hysteroscopy is direct endoscopic visualization of the endometrial cavity. Several studies indicates that hysteroscopy is highly accurate in diagnosing patients with endometrial cancer and moderately accurate in diagnosing other endometrial conditions in women with abnormal bleeding (Edward, et al. 2009).

2.6.6 Endometrial biopsy:

Endometrial biopsy is the most accurate method for diagnosis of endometrial cancer. Dilatation and curettage (D&C) is the gold standard method for diagnosis, newer and more sensitive method is the office based Pipelle device technique. Blind endometrial sampling techniques, such as the Pipelle, are most useful when the abnormality is global rather than focal (Edward, et al. 2009). Removing of tissue sample under control of hysteroscopy give the most accurate result, if neglected, false negative rates for the sample will range between 2 – 6 % (Karsten, et al. 2004).

2.6.7 Immunohistochemistry:

Immunohistochemistry (IHC) is an important tool used to investigate immune markers that are involved in endometrial carcinogenesis, allowing the early detection, diagnosis and assessment of these endometrial lesions (Sidonia, et al. 2011).

2.7 Treatment of endometrial cancer:
2.7.1 Surgery:
The standard treatment of endometrial cancer is surgical procedure. The initial treatment of endometrial cancer patients is done by total hysterectomy and bilateral salpingo-oophorectomy (TH/BSO), as well as pelvic and para-aortic lymphadenectomy. Operation may be either an open or a laparoscopic procedure. In patients with intra-abdominal disease (TAH/BSO) and maximal surgical debulking could be considered (Plataniotis and Castiglione. 2010).

2.7.2 Radiation therapy:
Radiation therapy (vaginal brachytherapy or external beam) is an effective treatment of patients with endometrial cancer. The use of radiotherapy is determined by age, tumor grade, depth of myometrial invasion, lymph node involvement and regional spread of the disease (Edward, et al. 2009).

2.7.3 Chemotherapy:
Chemotherapy is treatment of patients with advanced and metastatic endometrial cancer, patients with early stages of disease usually cured with surgery and radiotherapy. Chemotherapy may be either a single agent chemotherapy or multiple agents, however, the majority of patients are treated with multiple agents. Doxorubicin is the most widely used regimen, as single drug or in double and triple combination (Kimberly, et al. 2012).

2.7.4 Hormonal therapy:
Hormonal therapy (also known as endocrine therapy) is one of the most effective treatments of endometrial cancer. The endocrine method is associated with progesterone (PR) receptor expression, patients with high PR expression have high response rate, low PR expression leading to therapeutic agent resistance. Progestins are the most common agent used in endometrial cancer treatment (Qiong, et al. 2016).
2.8 Beta-catenin and its relation with endometrial cancer:

β-catenin is a multifunctional protein act as key element in two biological pathways, it coupled with E-cadherin to form cadherin-catenin complex that mediate cellular adhesion. β-catenin also function as oncogene in the Wnt signal transduction pathway. In normal cell, β-catenin phosphorylated and degraded in the cytoplasm. In cancer cell, transduction pathway disrupted causing intracellular accumulation of β-catenin, the accumulated β-catenin translocated into the nucleus that activate transcription pathway, constitutive transcriptional activation is associated with tumorigenesis (David, et al. 2006).

Abnormal or low expression of β-catenin is associated with the progression and metastatic potential of different epithelial tumors including breast, prostatic, gastric, thyroid and endometrial cancer (Ahmed and Eman. 2014).

Several studies reported that, β-catenin immunoeexpression was predominantly observed in normal proliferative endometrium while decreased in endometrial carcinoma, the expression tended to be reduced in histologically high grade tumors compared to low grade tumors (Hsien, et al. 2004).

Moreno et al reported that, β-catenin expression reduced in premalignant and malignant endometrial lesions. The immunoreactivity of β-catenin was more frequent in atypical hyperplasia compared to both endometrioid and non endometrioid endometrial carcinoma (Moreno, et al. 2003).

Peter et al reported that, the expression of β-catenin is associated with different histological variants of endometrial carcinoma. The study found that, expression of β-catenin was observed in (47%) of endometrioid adenocarcinomas but in none serous carcinomas. The study concluded that, the expression patterns of β-catenin in highgrade endometrial carcinomas is associated with the histology of the lesion (Peter, et al. 2002).
Chapter Three
Materials and Methods
Chapter Three
Materials and Methods

3.1 Materials:

Archived tissue blocks of endometrial tumors were selected for this study.

3.2 Methods:

3.2.1 Study design:

This is hospital based analytical retrospective case control study aimed to detect β- catenin expression in endometrial tumors.

3.2.2 Study sample:

Forty paraffin block samples were collected from patients previously diagnosed as endometrial tumor, 20 (50%) of them were malignant and the remaining 20 (50%) were benign. Clinicopathological characteristics of patients (age, histopathological diagnosis, malignant tumor grade) were obtained from patient’s records.

3.2.3 Study area:

This study conducted at Ribat University Hospital, Soba University Hospital, Omdurman Military Hospital and Sudan University of Science and Technology-college of medical laboratory science.

3.2.4 Sample processing:

One section was cut at 3μm from each tissue block by rotary microtome, mounted in positively charged slides and baked at 60°C for 30 minutes.

3.2.5 Immunohistochemical staining:

Immunohistochemical staining was carried out using new indirect-dextran polymer immune peroxidase technique. Tissue sections were deparaffinized in
xylene and rehydrated through graded ethanol solutions (100%, 90%, 70%, 50%) to water. The antigens were retrieved by using Dako PT Link with Tris EDTA buffer (pH 9) for 20 minutes and then cooling down to room temperature for 5 min. Endogenous peroxidase activity was blocked by peroxidase blocker for 10 minutes. The slide then treated with anti-human β-catenin primary antibody for 20 minutes at room temperature in a humid chamber, then washed in phosphate buffer saline (pH 7.4) for 3 minutes. Then sections incubated in dextran polymer- HRB (horseradish peroxidase) secondary antibody for 15 minutes then washed in three changes of phosphate buffer saline (pH 7.4), after that incubated in DAB substrate solution for 5 minutes, then washed in running water. Then counter stained in Mayer’s haematoxylin stain for one minute. After that dehydrated, cleared and mounted in DPX mounting media (Bancroft, et al. 2013).

3.2.6 Result interpretation:

All quality control measures were adopted, positive and negative control slides were used during immunohistochemical staining. Positive staining for β-catenin appeared as brown particles at the nucleus, nuclear membrane or in the cytoplasm. Under microscopy, 5 representative high-power fields (×40 magnification) per tissue section were randomly selected and evaluated. Detection of more than 5 cells with cytoplasm per one field considered as positive result.

3.2.7 Data analysis:

Data was analysed using SPSS 20 computer program. Frequency, mean, standard deviation and Chi-square test values were calculated.

3.2.8 Ethical consideration:

Samples were collected after taking ethical approval from each hospital to use the tissue blocks for research purposes.
Chapter Four

Results
Chapter four

4. Results

The present study includes forty samples, 20 (50%) samples of them were malignant and 20 (50%) samples were benign.

The age of study population ranged between 25 and 85 with a mean ± SD of 56.4 ± 14.9 years. Most of patients were older than 60 years representing 22 (55%) and the remaining 18 (45%) were younger than 60 years as showed in figure (4.1).

The histopathological diagnosis of study population includes 8 (40%) endometrioid adenocarcinoma, 6 (30%) papillary carcinoma, 5 (25%) squamous cell carcinoma, 1 (5%) malignant mixed mullerian tumor, 4 (20%) atypical hyperplasia, 16 (80%) non atypical hyperplasia as showed in table (4.1).

The tumor grade of study population includes 3 (15%) grade I, 6 (30%) grade II, 3 (15%) grade III, 8 (40%) not graded as showed in table (4.2).

Beta-catenin positive expression was found 13 (32.5%) in malignant samples, and 7 (17.5%) showed negative expression, while all benign samples 20 (50%) showed positive expression for beta-catenin. This result showed significant association (p. value = 0.004) as indicated in table (4.3), (4.4).
Figure (4.1): Frequency of age group among the study population
Table (4.1): Distribution of histopathological diagnosis among the study population

<table>
<thead>
<tr>
<th>Histological diagnosis</th>
<th>Type</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>Atypical hyperplasia</td>
<td>4</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td>Non atypical hyperplasia</td>
<td>16</td>
<td>80%</td>
</tr>
<tr>
<td>Malignant</td>
<td>Adenocarcinoma</td>
<td>8</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td>Papillary carcinoma</td>
<td>6</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>Squamous cell carcinoma</td>
<td>5</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td>Malignant mixed mullerian tumor</td>
<td>1</td>
<td>5%</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>40</td>
<td>100%</td>
</tr>
</tbody>
</table>
Table (4.2): Frequency of malignant tumor grade

<table>
<thead>
<tr>
<th>Grade</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>3</td>
<td>15%</td>
</tr>
<tr>
<td>Grade II</td>
<td>6</td>
<td>30%</td>
</tr>
<tr>
<td>Grade III</td>
<td>3</td>
<td>15%</td>
</tr>
<tr>
<td>Not graded</td>
<td>8</td>
<td>40%</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>100%</td>
</tr>
</tbody>
</table>
Table (4.3): Frequency of immunohistochemical result of β-catenin in endometrial tumors

<table>
<thead>
<tr>
<th>Immunohistochemical results</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>33</td>
<td>82.5%</td>
</tr>
<tr>
<td>Negative</td>
<td>7</td>
<td>17.5%</td>
</tr>
<tr>
<td>Total</td>
<td>40</td>
<td>100%</td>
</tr>
</tbody>
</table>
Table (4.4): Relation between histopathological diagnosis and β-catenin expression

<table>
<thead>
<tr>
<th>Histological diagnosis</th>
<th>β-catenin expression</th>
<th>P. value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Benign</td>
<td>20 (50%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Malignant</td>
<td>13 (32.5%)</td>
<td>7 (17.5%)</td>
</tr>
<tr>
<td>Total</td>
<td>33 (82.5%)</td>
<td>7 (17.5%)</td>
</tr>
</tbody>
</table>
Microphotograph (4.1): Non-keratinized squamous cell carcinoma of endometrium showed membranous positive expression of β-catenin (100X).
Microphotograph (4.2): Papillary adenocarcinoma of endometrium showed negative expression of β-catenin (100X).
Chapter Five
Discussion
Chapter five

5. Discussion

This study includes 40 samples of endometrial lesions stained by immunohistochemistry for beta-catenin. Considering the age group of study population, the study showed that the majority of cases were more than 60 years with a mean ± SD of 56.4 ± 14.9 years indicating that women with advanced age are more susceptible to endometrial cancer due to endogenous hormone level, genetic factors and family history. This result is consistent with Zhongfu et al. (2016), who reported that the risk of developing endometrial cancer increases with advancing age. Also agreed with Edward et al. (2009), who found that ninety percent of cases occur in women older than 50 years, and the median age at diagnosis is 62 years. This finding also agreed with Ahmed and Eman (2014), who reported that the majority of endometrial cancer patients were postmenopausal with the mean age 52 ± 12 years.

The histopathological diagnosis of study population revealed that the most frequent type was endometrioid adenocarcinoma. This result is consistent with Yalta et al. (2009), who reported that among the 32 cases of endometrial carcinoma, 23 of the malignant lesions were endometrioid adenocarcinoma, while nine were non endometrioid (papillary and clear cell carcinoma). Also agreed with Paulette et al. (2010), who reported that most frequent histological subtype was endometrioid adenocarcinoma (80%) of the cases.

Histological grading of malignant lesions were revealed in the study, the results showed that the more frequent grade was malignant tumors classified as grade II. This result is agree with Ahmed and Eman (2014), who reported that malignant tumor with grade II differentiation constitute the vast majority of malignant endometrial lesions. Also agreed with Paulette et al. (2010), who reported that grade II malignant tumor was the most frequent type.
In the present study β-catenin expression was detected in 65 percent of malignant lesions compared to 100 percent in benign lesions (p=004), our finding suggest that beta-catenin expression is more frequent in benign conditions. This finding is consistent with Hsien et al. (2004), who reported that the expression of beta-catenin in endometrial carcinoma decreased compared to that in benign endometrium. Also agree with Peter et al. (2002), who reported that beta-catenin expression was observed in 47 percent of endometrial carcinoma but in none of serous carcinoma (p=0.003).
Chapter Six
Conclusion and Recommendations
Chapter six

Conclusion and Recommendation

6.1 Conclusion:

On the basis of this study we concluded that:

- The age of endometrial cancer patients in Sudan is commonly more than 60 years.
- Most histological phenotype of endometrial cancer is endometrioid adenocarcinoma.
- Beta-catenin expression is associated with benign conditions of endometrial tumors.
6.2 Recommendations:

On the basis of the study we recommended that:

- Further study should be done for expression of β- catenin in endometrial tissue with large sample size.

- Beta-catenin should be used on panel of the epithelial markers to help in differentiation between benign and malignant endometrial tumors.
References


Appendices

Appendix 1:

Materials and instruments for processing and staining of the specimens, include:

- Disposable gloves.
- Rotary microtome.
- Microtome knives.
- Positively charged slides (Thermo).
- Cover glasses.
- Dry oven.
- Water path (Dako PT Link).
- Coplin jars.
- Humidity chamber.
- Ethanol (100%, 90%, 70%, 50%).
- Xylene.
- Mayer’s haematoxylin
  (Haematoxylin, DW, K or ammonium alum, sodium iodate, citric acid, chlormal hydrate).
- Tris EDTA buffer (pH 9).
- Phosphate buffer saline (pH 7.4).
- Peroxidase blocker
  (0.3% hydrogen peroxide).
- Primary antibody (Anti- Human β-catenin).
- Secondary antibody (dextran polymer conjugated secondary antibody-HRP).
- DAB(3, 3 diaminobenzidine tetrahydrochloride) substrate solution.
- DPX.
Appendix 2:

Monoclonal Mouse
Anti- Human
Beta-Catenin
Clone β-Catenin-1

Code M3539

ENGLISH

Intended use
For In Vivo Diagnostic Use

Dako Monoclonal Mouse Anti-Human Beta-Catenin, Clone β-Catenin-1 (Anti-beta-catenin, β-catenin-1) is intended for laboratory use to identify qualitatively by light microscopy β-catenin positive cells in normal and neoplastic tissues using immunohistochemical (IHC) test methods. The clinical interpretation of any positive staining or its absence should be complemented by morphological and histological studies with proper controls. Evaluations should be made within the context of the patient's clinical history and other diagnostic tests by a qualified individual.

Summary and explanation
The catenins are structurally related cytoplasmic proteins which have been classified as alpha (α), beta (β), and gamma (γ) according to their electrophoretic mobility.1,2 The β-catenin gene is located on chromosome 3p21 and encodes a 80 kD protein.2 This cytoplasmic protein is multi-functional, playing an essential role in the cadherin-mediated anchoring and organization of the cytoskeleton.2 Beta-catenin is also involved in regulation of gene expression as a mediator of the Wnt signaling pathway. Cellular β-catenin levels are tightly regulated by a multi-protein complex comprised of serine/threonine kinase GSK3β, the APC tumor suppressor gene product and axin, which facilitates phosphorylation and subsequent degradation of the β-catenin protein. Dysregulation of β-catenin degradation leads to cytoplasmic accumulation of the protein, followed by translocation to the nucleus. Nuclear β-catenin forms complexes with DNA binding proteins such as TCF and LEF, activating gene transcription.3

Refer to Dako’s General Instructions for Immunohistochemical Staining or the detection system instructions of IHC procedures for: 1) Principle of Procedure, 2) Materials Required, Not Supplied, 3) Storage, 4) Specimen Preparation, 5) Staining Procedure, 6) Quality Control, 7) Troubleshooting, 8) Interpretation of Staining, 9) General Limitations.

Reagent provided
Monoclonal Mouse antibody provided in liquid form as tissue culture supernatant is 0.05 mol/L Tris-HCl, pH 7.2 and 0.015 mol/L sodium azide. This product contains stabilizing protein.

Clone: β-Catenin-1
Isotype: IgG2, kappa

Mouse IgG concentration mg/mL See label on vial.

M3539 may be used at a dilution of 1:200 when performing IHC using the EnVision+ DAB (code K4005) detection system. These are guidelines only.

Optimal antibody concentrations may vary depending on specimen and preparation method, and should be determined by each individual laboratory.

Immunogen
Recombinant C-terminal β-catenin-GST fusion protein

Specificity
Anti-beta-catenin, clone β-catenin-1 recognized human β-catenin protein in Western blots of human epithelial A431 cells and mouse β-catenin in blots of mouse fibroblast NIH3T3 cells. No cross-reactivity with α and γ-catenin was observed.3

Materials required, but not supplied
Refer to Dako’s General Instructions for Immunohistochemical Staining and/or the detection system instructions. Suggested diluent for IHC procedures:

Dako Antibody Diluent (code SB809).

The following negative control is recommended for IHC procedures:

Mouse IgG1 (code X0001).

Precautions
1. For professional users.
2. This product contains sodium azide (NaN₃), a chemical highly toxic in pure form. At product concentrations, though not classified as hazardous, NaN₃ may react with lead and copper plumbing to form highly explosive build-ups of metal azides. Upon disposal, flush with large volumes of water to prevent metal azide build-up in plumbing.4
3. As with any product derived from biological sources, proper handling procedures should be used.
4. Wear appropriate Personal Protective Equipment to avoid contact with eyes and skin.
5. Unused reagents should be disposed of according to local, state, and federal regulations.

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35
Storage
Store at 2–8 °C. Do not use after expiration date stamped on vial. If reagents are stored under any conditions other than those specified, the conditions must be verified by the user. There are no obvious signs to indicate instability of this product. Therefore, positive and negative controls should be run simultaneously with patient specimens. If unexpected staining is observed which cannot be explained by variations in laboratory procedures and a problem with the antibody is suspected, contact Dako Technical Support.

Specimen preparation
Paraffin sections
Anti-beta-catenin, beta-catenin-1 can be used on formalin-fixed, paraffin-embedded tissue sections.

The deparaffinized tissue sections must be treated with heat prior to the IHC staining procedure. Target retrieval involves immersion of tissue sections in a pre-heated buffer solution and maintaining heat, either in a water bath (95–99 °C) or in a steamer (95–99 °C). For greater adherence of tissue sections to glass slides, the use of sterilized slides (Code: S3002) is recommended. Target Retrieval Solution code S1705 or Dako Target Retrieval Solution (code S1690) is recommended using a 20-minute heating protocol.

Cryostat sections and cell smears
Anti-beta-catenin, beta-catenin-1 can be used for labeling acetone-fixed cryostat sections or fixed cell smears. Target or antigen retrieval is not required.

Staining procedure
Follow the recommended procedure for the detection system selected.

Staining interpretation
The cellular staining pattern of anti-beta-catenin is mainly membranous, especially at the cell-cell boundaries. Positive nuclear staining and diffuse cytoplasmic staining have been reported in cancer cells. 1,2

Performance characteristics
Normal tissues
Beta-catenin expression has been demonstrated in the membrane of normal epithelium. In normal urothelium, expression was found to be uniformly strong at the intercellular borders. More pronounced staining was observed at the apical junctional complexes of the superficial cell layer, whereas there was no expression at the luminal membrane and parts of the cells in contact with the basement membrane (frozen and paraffin). 3,4 In normal breast epithelium, normal ductal cells of breast within the lobular units stain in a peripheral and cytoplasmic pattern. In normal mammary ducts and acini, beta-catenin strongly localized to the basolateral surfaces of luminal epithelium; weak immunostaining was observed at lateral borders of myoepithelial cells (paraffin). 5 In normal colonic mucosa, beta-catenin immunoreactivity was observed along the intercellular borders of all epithelial cells; no immunoreactivity was seen at the basal side facing the basement membrane or at the luminal cell border (frozen and paraffin). 3,6 Expression of beta-catenin, although present everywhere except in parakeratinized cells of normal esophageal epithelium, was more marked in the prickle cell layer than in the basal and parakeratinized layers. 6 In gastric epithelium, beta-catenin immunoreactivity was in a membranous distribution throughout the epithelium of gastric crypts and glands, with increased intensity in deeper parts of enteral, body, and cardiac glands. 3,2,7,8 Cytoplasmic and nuclear staining in normal gastric mucosal epithelium has also been observed (paraffin). 9 Normal thyroid follicular cells showed immunoreactivity mainly at cell-cell contacts, with the cytoplasm being weakly reactive (paraffin). 3

Weak membrane-localized immunoreactivity has also been observed in endothelial cells, muscle cells, and neurons (paraffin). 10,11,12

Abnormal cells
Beta-catenin expression has been demonstrated by immunohistochemistry in a variety of tumors. Neoplasms which have demonstrated positive immunoreactivity for beta-catenin include: bladder transitional cell carcinoma, colon adenocarcinoma and adenomas, breast adenocarcinoma, esophageal squamous cell carcinoma, primary squamous cell carcinomas of the head and neck, stomach adenocarcinoma, ovarian carcinoma and thymus carcinoma. 9 In some studies abnormal beta-catenin expression (weak, low percent positive cells or nuclear and cytoplasmic localization) has been associated with clinicopathological features such as high histological grade and metastases. 3,13,14,15,16

FRANÇAIS
Ref. M308
Utilisation prévue
Pour utilisation in diagnostic in vitro


Résumé et explication
Les catézines sont d'un point de vue structural, apparentées aux protéines cytoplasmiques et ont été classifiées comme alpha (α), beta (β), et gamma (γ) en fonction de leur mobilité électrophorétique. 17 Le gène de la β-catézine est localisé au niveau de la région chromosomique 3p22 et code pour une protéine de 69 kDa. 18 Cette protéine cytoplasmique a de multiples fonctions, jouant un rôle essentiel dans l'ancrage adhésif par les cadhérines et dans l'organisation du cytosquelette. 19 La β-catézine est également impliquée dans la régulation de l'expression génique comme un médiateur de la voie de signalisation Wnt. Les niveaux de β-catézine cellulaires sont étroitement régulés par un complexe multicomposant comprenant la sécrétion de la protéine β-catézine. 9,20 Le produit du gène sécréteur de l'affecte, qui facilite la phosphorylation et la dégradation ultérieure de la protéine β-catézine. 20 Un déséquilibre de la dégradation de la β-catézine conduit à une accumulation cytoplasmique de la protéine, suivie par una translocation vers le noyau. La β-catézine nucléaire forme des complexes avec des protéines liées à l'ADN telles que le TCF et le LEF, activant ainsi la transcription de gènes. 21,22

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(schwach, geringer Prozentsatz positiver Zellen oder nucleare und/oder zytosomatische Lokalisation) mit klinisch-pathologischen Merkmalen, wie z.B. einem höheren histologischen Grad und Metastasen, assoziiert.

References

1. Antibody Certification, OncoZyme


