



Original Research Article

Adiponectin levels in patients with endometrial carcinoma and abnormal uterine bleeding

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ABSTRACT

Introduction: The current age lifestyle changes and increasing obesity in India has led to increased incidence of endometrial cancer. With the increasing survival rates of cancer confined to uterus, numerous tumour markers have been tried for early diagnosis of endometrial cancers. Adiponectin has been linked to obesity related cancers. Low levels of Adiponectin are suspected to be a risk factor for the development of endometrial cancer. But there are contradictory results reported by few researchers. Hence this study was designed to identify whether adiponectin can differentiate endometrial carcinoma and abnormal uterine bleeding (AUB), as AUB is commonest presentation in patient with endometrial carcinoma.

Objectives: To estimate and compare serum adiponectin levels in patients with endometrial cancer and AUB.

Materials and Methods: This observational study included thirty eight patients with endometrial carcinoma and 40 BMI matched patients with AUB as study subjects. Endometrial carcinoma and AUB were diagnosed by Ultrasound scanning, Endometrial biopsy and histopathological examination. Blood samples were collected from all study subjects after informed written consent. Serum adiponectin were estimated by Enzyme Linked Immunosorbent Essay (ELISA).

Results: The mean adiponectin level for endometrial cancer cases was 12.6 $\mu\text{g/mL}$ and mean in AUB group was 12.2 $\mu\text{g/mL}$.

Conclusion: Serum Adiponectin levels did not significantly vary in patients with Endometrial carcinoma and AUB. The estimation of adiponectin did not differentiate endometrial carcinoma and abnormal uterine bleeding patients.

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1. Introduction

Endometrial carcinoma (EC) is the most common gynecological malignancy in Western and developed countries. The incidence rate of EC in India was estimated as 105.5 per 1,00,000 women. Although the incidence of endometrial carcinoma is comparatively low in India, there is increasing incidence of risk factors for the development of endometrial carcinoma such as obesity and metabolic syndrome. More

cases of Endometrial Carcinoma are reported in urban areas of India due to the life style changes and urbanization.¹

Obesity is well known risk factor for endometrial cancer and it increases the risk of EC up to 17–46% in postmenopausal women. According to the previously published data, BMI remained a significant risk factor for the development of endometrial cancer. BMI $\geq 32 \text{ kg/m}^2$ and BMI $\geq 35 \text{ kg/m}^2$ associated with increased risk of developing endometrial cancer with relative risk of 4 and 6, respectively.^{2,3} The unopposed action of estrogen is the main reason for the development of EC. Obesity and its

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associated systemic inflammation with insulin resistance also included in the mechanism of endometrial cancer development and disease progression.⁴

Few studies have shown the relation of adiponectin, an insulin sensitising adipokine in endometrial carcinoma development. Low level of adiponectin is inversely associated with Insulin resistance and obesity, which are also related to Endometrial cancer. Petridou et al. showed that low adiponectin levels increases the risk of endometrial cancer.⁵ Previously published study by Barb D et al showed that low plasma adiponectin levels are independent risk factor for EC even after adjusting BMI, age, Diabetes and Hypertension.⁶ The European Prospective Investigation into Cancer and Nutrition (EPIC) Study, a large prospective nested case-control study confirmed the relation between lower pre-diagnostic plasma adiponectin concentrations and a higher risk of endometrial cancer in both pre-and postmenopausal women regardless of BMI status or other obesity-related risk factors.⁷ There are studies showed conflicting results to these findings.^{8,9}

Abnormal uterine bleeding (AUB) is most common presentation of many gynaecological conditions including EC. Since obesity and insulin resistance are considered as a risk factor for the development of endometrial cancer, this study was aimed to estimate the levels of adiponectin in endometrial cancer patients in comparison with AUB patients at tertiary care hospital in Southern part of India.

2. Materials and Methods

This Observational study was conducted in the Department of Biochemistry in collaboration with Department of Obstetrics and Gynaecology, Jawaharlal Institute of Post graduate Medical Education and Research (JIPMER), Puducherry, India. The study was approved by JIPMER research committee and Institute Ethics sub-Committee.

2.1. Patients and subject enrolment

The subjects were enrolled into two groups according to study criteria. Histopathologically diagnosed cases of endometrial cancers were included into group 1, whereas group 2 included BMI matched cases of AUB other than endometrial cancers. The AUB cases were diagnosed after endometrial biopsy or Ultrasound scanning. The intention behind adding group 2 with AUB patient is to estimate the levels of adiponectin in patients having similar symptoms like Endometrial carcinoma and to find out whether adiponectin levels can be able to differentiate these two conditions. Women who were on hormone replacement therapy, patients with abdominal tuberculosis and diabetes mellitus were excluded from the study.

Thirty eight subjects with endometrial cancer and forty BMI matched subjects with AUB other than endometrial cancers were enrolled into group 1 and 2 respectively.

Informed consent was obtained from each study subjects.

2.2. Assessment of risk factors and estimation of adiponectin

Body mass index (BMI) was calculated by measuring height and weight of the patients using the formula,¹⁰

$$BMI = \frac{Weight (Kg)}{[Height (m)]^2}$$

BMI was expressed as kg/m². Five ml of blood was collected from all women in the study group and serum was separated. Serum adiponectin levels were measured by commercially available ELISA kits (Ani Biotech Oy, Origenium Laboratories Business Unit, Finland). It was measured by solid phase quantitative sandwich ELISA method with inter assay precision is $\leq 12\%$ and intra assay precision is $\leq 10\%$.

2.3. Statistical analyses

Data were expressed as mean with standard deviation for the normally distributed data. Parametric variables of two groups were compared by independent t test. Statistical analyses were performed at 5% level of significance using Statistical Package for Social Sciences (SPSS) 20 software and p value ≤ 0.05 was considered significant.

3. Results

A total of 38 subjects were included in group 1. Forty BMI matched cases of abnormal uterine bleeding other than endometrial cancer was included into group 2.

The mean age of patients with Endometrial carcinoma was 49.8 ± 7.2 years and patients with AUB were 48.3 ± 4.5 years. This difference is not statistically significant. Results are shown in Figure 1.

The mean of BMI in Endometrial Carcinoma patients were 26.4 ± 5.7 kg/m² and AUB patients were 25.4 ± 5.1 kg/m². There are no significant differences in height, weight and BMI between both the study groups as they were matched. Results are shown in Figure 2.

Among our study group 1, majority of cancer (95%) were of endometrioid adenocarcinoma type on histopathological analysis. This group also include one each case of uterine papillary serous carcinoma and poorly differentiated carcinoma. Menopausal status of the patients in both the groups was matched.

Adiponectin levels were compared between two groups and there was no statistically significant difference in the levels of serum adiponectin between groups. Results are given in Table 1 .

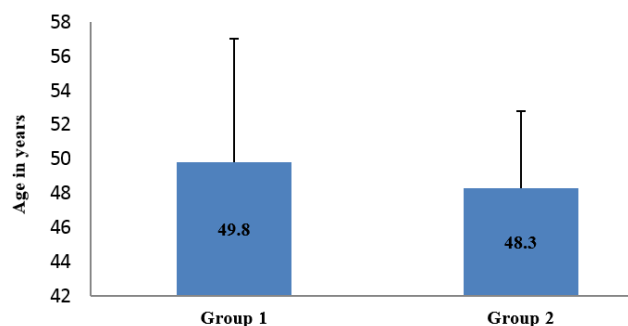
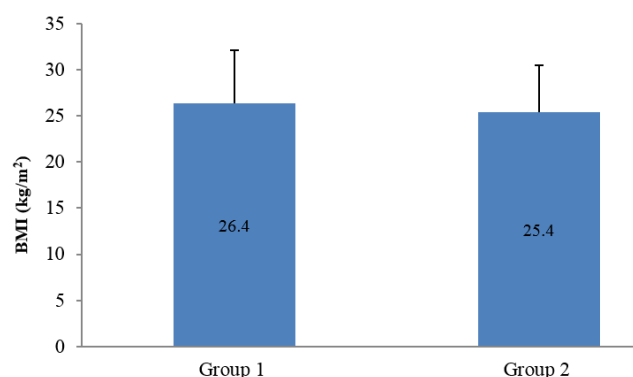
4. Discussion

Obese subjects have not only increased risk of developing cancer but also their mortality is increased with increasing BMI. More specifically, obesity is proved to be one of

Table 1: Comparison of Adiponectin levels in patients with endometrial cancer (group 1) and abnormal uterine bleeding (group 2)

Variable	Group 1 (n = 38)	Group 2 (n = 40)	p value
Adiponectin ($\mu\text{g/mL}$)	12.6 \pm 0.9	12.2 \pm 1.0	0.07

Values are expressed as Mean \pm SD

**Fig. 1:** Comparison of mean age between the patients with endometrial carcinoma (group 1) and abnormal uterine bleeding (group 2)**Fig. 2:** Comparison of BMI between the patients with endometrial carcinoma (group 1) and Abnormal uterine bleeding (group 2)

the risk factors for cancers among women in various organs including Endometrium, Breast, Colon, Rectum, Oesophageal, Kidney, Pancreas, Ovarian, Cervix and Liver. This is due to the elevated levels of endogenous Estrogen in obese women and the rate of production of estrogenic compounds is related to the amount of adipose tissue.¹¹

There are convincing evidences for a cancer preventive effect of avoidance of weight gain or weight loss in endometrial cancer in humans and also many studies in animal model showed that calorie restriction dramatically reduced spontaneous and carcinogen induced tumour development.^{11,12}

Adiponectin plays an important role not only in glucose, lipid metabolism but also altered adiponectin levels are involved in the progression of various types

of cancers. Adiponectin has a longer half-life than most polypeptide hormones and circulating levels are not affected significantly by either fasting or food intake.¹³ There are accumulating evidences indicate that adiponectin measurements may serve as a useful screening tool in predicting the risk or for early detection of obesity related cancers. *In-vitro* studies have proved that adiponectin inhibits the proliferation of endometrial cancer cells.¹⁴

The most frequent symptom of endometrial cancer is Abnormal uterine bleeding but is also seen in other gynecological disorders. The probability of endometrial cancer in women presenting with postmenopausal bleeding is 5 – 10%, but the chances increase with age and risk factors. Since this cancer is related to obesity and insulin sensitivity, Adiponectin could serve as a marker to diagnose EC. Previous studies have stated that a reduced level of adiponectin in patients with EC when compared to normal patients.^{6,7} But very few studies investigated the role of tumour makers to differentiate gynecological malignancies from their benign conditions.^{15,16}

The study by Maso *et.al* have showed that adiponectin is inversely associated with risk of endometrial cancer; in addition, women with high BMI and low plasma adiponectin have a 6.5-fold higher risk of endometrial cancer than women with normal BMI and higher adiponectin concentrations.¹⁷ The beneficial action of adiponectin is through activation of the AMPK pathway which suppresses cell proliferation.¹⁸ Previous studies have proved that increased circulating plasma adiponectin level were protective factor in preventing the development of endometrial cancer.^{7,19,20}

A meta-analysis by Lin T *et al* with 12 prospective studies proved an inverse relationship between plasma adiponectin levels and endometrial carcinoma risk in postmenopausal women but not in premenopausal women. They also showed that there is dose response relationship between adiponectin levels and endometrial carcinoma risk.²¹

In this study we did not get statistically significant difference in the level of serum adiponectin between two groups. Many previous studies have compared this adipokine level in endometrial carcinoma patients and normal controls and showed the significant difference due to the differences in BMI in study subjects. Since Adiponectin related to body weight and fat mass, we compared the adiponectin levels in BMI matched AUB patients

Few studies have also proved that there was no correlation between adiponectin and endometrial cancer.^{8,9}

Soliman PT *et al* conducted a Prospective nested case-control study within the Nurses' Health Study with 144 cases of endometrial cancer patients and compared the levels of adiponectin with control group. The mean adiponectin level for cases was $12.88\mu\text{g/mL}$ and mean in the control group was $12.85\mu\text{g/mL}$. Most of the women in case group are in the premenopausal stage and they have concluded that there is no association with prediagnostic adiponectin levels and endometrial carcinoma risk.⁸

Dallal *et al* estimated total and high molecular weight adiponectin levels in nested case-control study with long duration of follow-up which involved 66 endometrial cancer patients and 124 control subjects. The median of total adiponectin levels in cases and controls are $14.3\mu\text{g/ml}$ and $14.6\mu\text{g/ml}$ respectively and showed that there was no correlation between endometrial cancer and adiponectin levels which also resembles our study results.⁹

5. Conclusion

Serum Adiponectin levels did not significantly vary in patients with Endometrial carcinoma and abnormal uterine bleeding. In our study, estimation of adiponectin alone did not differentiate endometrial carcinoma patients from abnormal uterine bleeding patients. Therefore, estimation of serum adiponectin may be combined with other tumour markers to improve the strength of pre-operative screening of Endometrial Carcinoma. However, further studies are needed in large scale to confirm the role of adiponectin in the screening of Endometrial carcinoma.

6. Limitations

1. The only adipokine, Adiponectin was measured
2. Normal healthy women were not included as comparison group and it will be included in future studies.

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9. Informed consent

Informed consent was obtained from all individual participants included in the study.

10. Conflict of interest

No conflict of Interest.

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