



DIABETES MELLITUS AND RISK OF ENDOMETRIAL CARCINOMA

KEYWORDS

Endometrial Carcinoma, Diabetes Mellitus, Post Menopause, Staging Laparotomy

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ABSTRACT

Introduction: Cancer endometrium is now emerging as the most common female genital carcinoma. Exposure to higher levels of endogenous or exogenous estrogens plays a major role in endometrial carcinogenesis. Approximately 75% of endometrial carcinoma are postmenopausal and 25% premenopausal or perimenopausal

Aim: This retrospective case study was undertaken to identify diabetes as a major metabolic risk factor for endometrial cancer.

Materials & methods: This study was conducted at Govt ISO and Kasturba Gandhi Hospital for Women and Children, Madras Medical College, Chennai-05 on 44 cases of cancer endometrium confirmed histologically for a duration for 36 months(3yrs) from January 2014 to December 2016.

Discussion & conclusion: This study shows a consistent positive association between diabetes and endometrial cancer almost two times risk exaggerated by obesity & sedentary habits four fold and finally 10 fold risk if all metabolic factors were present.. Interventions to reduce body weight and increase physical activity may have important implications in terms of prevention of endometrial cancer.also prompt and early management of diabetic patients with proper diet and drugs and early diagnosis of cancer endometrium

INTRODUCTION:

Cancer endometrium occupies the fourth position in women malignancies next only to breast malignancy and most common female genital malignancy in developing world. Overall morbidity and mortality has become less because it can be identified earlier. Age adjusted rates of endometrial cancer are increasing in countries undergoing transition from low to high socio economic status (15 /100 000 in North America to 5 /100 000 in Asia).In India the incidence is 4.3 /100 000.

Exposure to higher levels of endogenous or exogenous estrogens plays a major role in endometrial carcinogenesis. Approximately 75% of endometrial carcinoma are postmenopausal and 25% premenopausal or perimenopausal .Any abnormal bleeding during perimenopause has to be evaluated. Familial and genetic predisposition is suggested by its association with other primary cancers outside the uterus. Median age 63 yrs with more than 90% occurring after age 50 and 4% occurring less than 40. **INCIDENCE** of cancer endometrium is 5.2/100 000 (Delhi) to 3.2/100 000 (Bangalore). Five year survival rate more is than 95% for early and 68% for regional spread and 17% if distant disease had occurred. Lifetime risk of 2.8% will be diagnosed with endometrial cancer at some point during their lifetime. Mortality rate is approximately 1.7-2.4 per 100 000.

Estimated (new cases) in 2016 400,000 women and death in 82000 women. (20.5%)

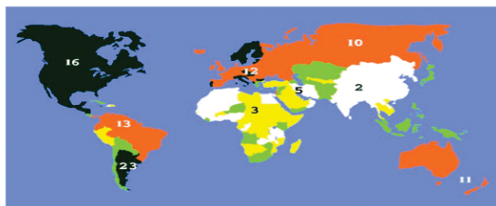


Fig 1. GLOBAL INCIDENCE OF CANCER UTERUS INCIDENCE- age standardized rates (ASR)/100 000.

RISK FACTORS : Risk factors are consistently associated with development of endometrial carcinoma which include family history, increasing age, postmenopausal ,diabetes(more risk with

increased -BMI and waist hip ratio- WHR) hypertension, dyslipidemia, obesity with reduced physical activity, early menarche(<12 yrs), late menopause(>52 yrs) ,menstrual disorders, gall bladder and liver disease, Endometrial hyperplasia Endometrial polyp, hypothyroidism and PCOS (anovulation), and exogenous unopposed estrogen exposure(HRT), tamoxifen given for breast malignancy.

Lactation, OCPs,(more than 5yrs reduces risk by 50%-weiderpass et al study),low fat diet, good physical activity decrease the risk of cancer endometrium.

METABOLIC SYNDROME:

Us national cholesterol Education Programme adult treatment panel (NCEP)-atleast 3 of the following:

1. Central obesity/elevated waist circumference, hypertension, high TGL, low HDL cholesterol, impaired fasting glucose(type 2 dm)

IDF(international diabetes foundation)

Central obesity/elevated waist circumference plus-any two factors Impaired fasting glucose, hypertension, low HDL cholesterol, high TGL

Large amount of epidemiological evidence on the association of **diabetes and female cancers** like breast and endometrial cancers.. There is accumulating evidence that hyperinsulinemia, in the context of insulin resistance, is associated with carcinogenesis.

1. **Hyperinsulinemia** through decreasing levels of insulin-like growth factor (IGF)-binding protein-1 and IGF-binding protein-3 increases **circulating free IGF-I**, which by binding and activating IGF-I receptors in the endometrium stimulates cell proliferation and inhibit apoptosis, thus contribute to tumor promotion and metastasis

2. **Hyperinsulinemia** may also increase levels of **free estrogens** through decreasing concentrations of circulating sex hormone-binding globulin. Estrogens have in turn shown to increase endometrial cancer risk by stimulating proliferation of endometrial cells when unopposed by progesterone (especially in post menopausal ladies).

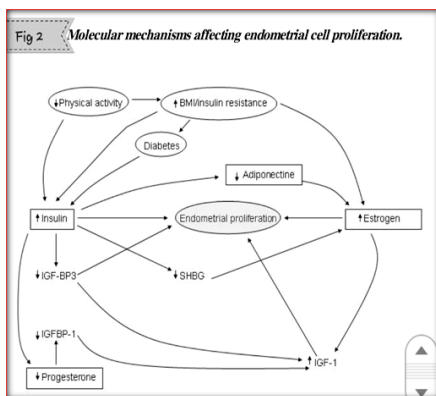
3. **Insulin** is shown to stimulate the growth of endometrial stromal cells by binding to insulin receptors on endometrial cells and studies have observed an elevated risk of endometrial cancer in relation to high pre diagnostic C-peptide concentrations indicating hyperinsulinemia.

4 **Low adiponectin concentrations**, a novel endogenous insulin sensitizer, are not only associated with higher levels of hyperinsulinemia /insulin resistance but may also directly alter cell proliferation/apoptosis and angiogenesis by a process that involves members of the **caspase group of apoptotic enzymes**.

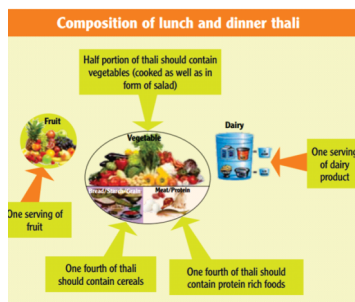
5. **Diabetic-therapeutic dose of metformin** acts on endometrial cancer cell proliferation by downstream targets of the adenosine monophosphate-activated protein kinase (AMPK)/mammalian target of rapamycin (mTOR) and mitogen-activated protein kinase (MAPK) pathways and possesses antineoplastic properties, such as improving response rates to neoadjuvant chemotherapy.

MOLECULAR MECHANISM OF DIABETES CAUSING ENDOMETRIAL CARCINOMA:

According to glycobiology, some glycans and their alterations in glycosylations are involved in the fundamental molecular and cell biology processes occurring in cancer such as cell signaling, communication, tumour cell dissociation and invasion, cell to cell matrix interactions, tumour angiogenesis, immune modulations, metastasis formation.



In many prospective cohort studies, women with diabetes had a statistically significant 2-fold higher risk for developing endometrial cancer. The risk was increased 3-fold among obese diabetic women with physical activity and 6- fold in obese diabetic women without physical activity. Further the risk was 10-fold if other metabolic syndromes like hypertension, dyslipidemia and hypothyroidism were combined. Thus obesity and physical activity are two modifiable risk factors for diabetes thereby affecting cancer endometrium.



National Guidelines for Diagnosis & Management

HYPERTENSION:

This acts as a risk factor for carcinoma endometrium by inhibiting apoptosis and contributing to tumorigenesis.

HYPOTHYROID AND PCOS:

Both of these by providing a consistent anovulatory environment contribute to genesis of carcinoma endometrium (Hyperestrogenic environment)

ENDOMETRIAL HYPERPLASIA AND CANCER:

Endometrial hyperplasia is divided into two groups (1) hyperplasia without atypia (2) hyperplasia with atypia according to 2014 WHO classification. The risk of hyperplasia without atypia progressing to malignancy is less than 5% over 20 years, patients are reassured. Risk of Hyperplasia with atypia progressing to malignancy is nearing 25%, these patients are placed as high risk, harbouring premalignant lesion and managed carefully by advising proper conservative or hysterectomy with BSO if warranted.

Two types of endometrial carcinoma are distinguished with respect to biology and clinical course. Type -1 carcinoma related to hyperestrogenism by association with endometrial hyperplasia, frequent expression of estrogen and progesterone receptors and younger age

Whereas type -2 carcinoma unrelated to estrogen, associated with atrophic endometrium and lack of estrogen receptors, old age. Histologically endometrioid and mucinous carcinomas are considered as type 1 and serous and clear cell carcinomas type 2. Recently genetic alterations are taken into account and thus in type 1-PTEN, K-ras, and finally P53 mutations occur and in type -2, initially P53 mutations followed by her2/neu mutations occurs.

AIM OF STUDY:

This study was undertaken to identify diabetes as a major metabolic risk factor for endometrial cancer. This study also has important public health implications in terms of endometrial cancer prevention by early identification and treatment of diabetes, early identification of endometrial carcinoma and modifying the associated high risks like obesity and physical activity.

MATERIALS:

This retrospective case study was conducted at Govt Iso and Kasturba Gandhi Hospital For Women And Children, Madras Medical College, Chennai-05 on 44 cases of cancer endometrium confirmed histologically for period of 36 months(3yrs) from January 2014 to December 2016.

The study was approved by Hospital Ethical Committee.

INCLUSION CRITERIA:

1. All patients with cancer endometrium and diabetes mellitus
2. All patients with cancer endometrium and hypertension, obesity, dyslipidemia, hypothyroid, pcso
3. All patients with cancer endometrium and post menopausal bleeding
- 4 All patients with cancer endometrium other ovarian and cervical malignancies

EXCLUSION CRITERIA:

1. Cancer endometrium patients with distant metastasis.
2. Cancer endometrium patients already operated and under follow up.

METHODOLOGY:

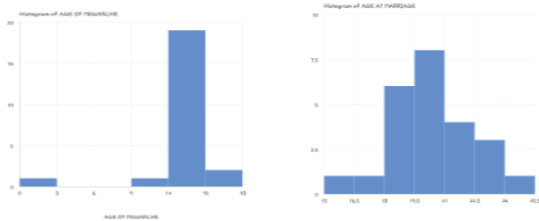
- Detailed history of the patient including name, age, socio-economic status, age at menarche, marriage, first and last child birth, parity, post menopausal years, family history of breast and other genital malignancies. history of diabetes mellitus, hypertension, dyslipidemia, hypothyroidism, pcso, obesity,

post menopausal bleeding, histopathology of cancer endometrium done outside was asked.

- All patients presenting complaints, associated symptoms, similar episodes in past, referral ultra sonograms and other imaging, fractional curettage reports done outside were meticulously noted
- Clinical examination including build, nourishment, BMI, anemia, pedal edema, generalized lymphadenopathy (supraclavicular nodes), cardio respiratory, and local examination including speculum, per vaginal and per rectal examination were completed for each case.
- Basic investigations, **fasting .post prandial blood sugar**, thyroid profile, VIA-VILI, pap smear, colposcopy, **USG, CECT,MRI, tumour markers-ca125, -hcg** was done for required patients
- After **diabetologist**, cardiologist, anesthetist and **surgical oncologist** opinion patients were subjected to Fractional or **hysteroscopic** curettage and were planned for major STAGING LAPAROTOMY(TAH WITH BSO AND LYMPH NODE SAMPLING WITH OMENTECTOMY and final HPE was obtained and further follow up with surgical medical, radiation oncologist was done.

RESULTS:

Mean age at menarche and marriage were 13 and 22 yrs respectively in our study. The average age at first childbirth and last child birth were 24 years and 30 years respectively. The average age at presentation for carcinoma endometrium in our study is 57.5 yrs. **DIABETES IS ASSOCIATED IN 23 CASES (52%) OUT OF 44 CASES of cancer endometrium thus contributing as a major risk factor.**



Ranges from 1 ("50") to 15 ("65 YRS" and "63RS"), with most values at the high end. The median is 13.

Ranges from 16 ("55YRS") to 24 ("65 RS").

Chart 1

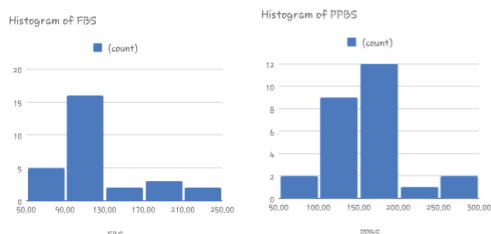


Ranges from 20 ("63", "58YRS", "58 YRS" and "58YRS") to 26 ("64").

Ranges from 8 ("DHANALAKSHMI" and "DEIVATHY") to 45 ("LAKSHMI"). but most values are around 25.6, plus or minus 6.41.

Ranges from 24 to 40.

Chart 2



Ranges from 65 ("9.66M%, PLT-2.25 LAK") to 245 ("HB-9.66M%, PLT-2.7L"), with most values at the low end. The median is 112.

Ranges from 98 ("96M%, PLT-2.2L" and "HB-9.06M%") to 280 ("HB-9.96M%, PLT-2.9L"), with most values at the low end. The median is 163.

Chart 3

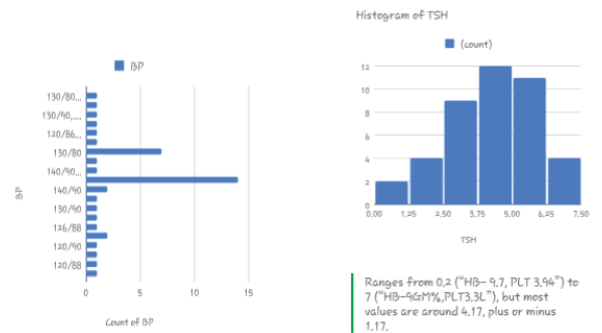


Chart 4

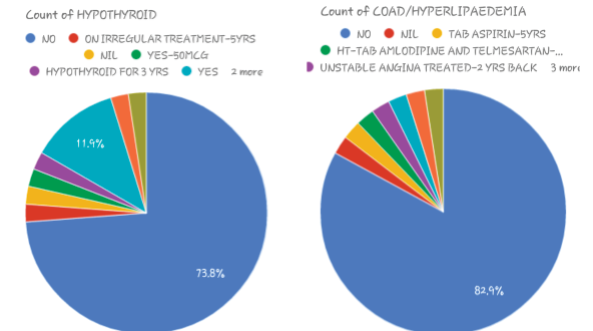


Chart 5

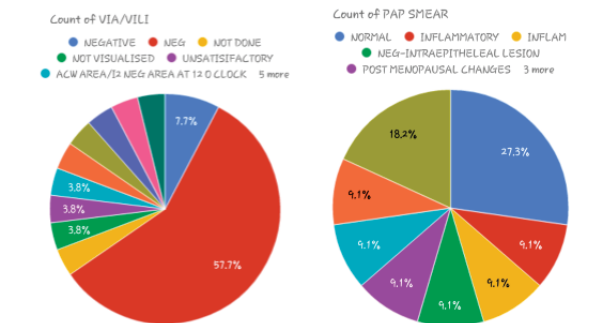


Chart 6

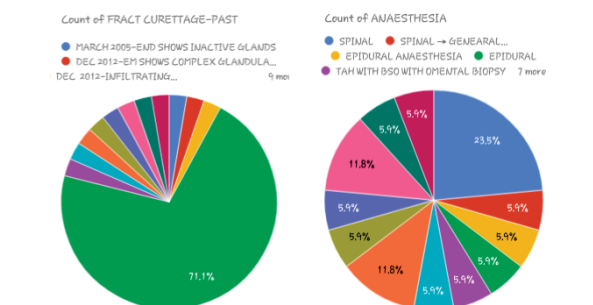


Chart 7

DISCUSSION:

Average age of patients in our study is 57.5 yrs (shehan et al study where the incidence was 56 yrs). Most of the patients were cooly 92% and only 8% were admitted in payment ward. Among the total cases, urban origin were 28 (63 %) and rural 16 (36%). (Milurich et al study ,shows urban 69% and rural 31%)

Average age at menarche	12.6 yrs
Average age at marriage	22 yrs
Average age at first childbirth	23 yrs
Average age at last child birth	33 yrs

In our study 28 cases were sterilised, one had undergone vasectomy

and 13 were not sterilised. 24 patients had irregular cycles and 22 had regular cycles.

Premopause	11 cases					30%
Postmenopause		<5yrs	5-10 yrs	10-20 yrs	>20 yrs	
	33cases	4 cases	5 cases	6 cases	13	70%

BMI	<18	18-25	25-30	>30
N=44 CASES				
No of cases	10	8	15	11
Percentage	22%	18%	34%	25%

The above is in accordance with sheman et al study showing same percentage

Among 44 cases 11 cases had a scarred abdomen. No patients had enlarged supraclavicular nodes. One patient had inguinal node enlarged .One patient had history of breast malignancy with a mastectomy scar on right side.

Diabetes mellitus was associated in 23 cases of carcinoma endometrium (out of 44 cases taken for study). This accounts for 52.2% , a very strong association that is more than half of total cases.(Mirham et al study shows 49.8% association).

New onset DM	DM for<5yrs	Dm for 6-10 yrs	Dm >10 yrs	IGT
6 cases	8 cases	5 cases	4 cases	6 cases

Type 1 diabetes in 4 cases and type 2 diabetes in 40 cases. History of PCOS in 9 cases (regular cycles in 6 cases and irregular cycles in 3 cases)

Meal plan	Insulin newly started	Already on insulin	OHA
10 cases	4 cases	11 cases	9 cases

We diagnosed diabetes depending on the values of fasting, post prandial blood sugars and glycaemic Diabetologist opinion obtained for all cases and after only strict control of blood sugars we posted them to minor and major procedures.

	New onset	<5yrs	6-10 yrs	Total	percentage
Hypertension	4	5	7	16	36%
Hypothyroid	3	4	3	10	22%

	No of case	percentage
DM + HT	12 cases	27%
DM + hypothyro	9 cases	20%
DM +HT + hypot	6 cases	13%

History of OCPs intake in 4 cases (one for 6 months, two patients for 1 yrs, one patient for 2 yrs)

N=44 CASES	Pre menopausal bleeding	Peri menopausal bleeding	Post menopausal bleedin	White discharge	Lower abd pain/myalgia	Urinary/bowel disturbance
No of cases	10	6	28	14	10	3
Percentage	22%	13%	63%	31%	22%	6%

The patients referred with fractional and hysteroscopic finding of cancer endometrium was 10 and 3 cases were referred with complex hyperplasia with atypia and five with proliferative phase. Patients referred with thickened endometrium were 16 in number, five cases with ET>2.5cm with mass lesions and many patients (11 cases) were referred with CT/MRI of suspicious endometrial masses favouring carcinoma endometrium. VIA -VILI and PAP SMEAR done for all of our patients.

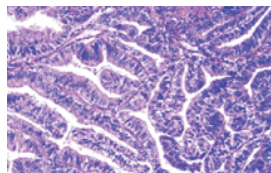
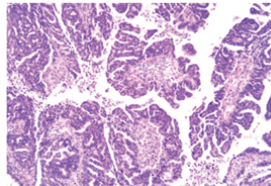
Hysteroscopy done for 19 patients. Hysteroscopy of one such patient with endometrial pulsating polyp with foci of endometrial malignancy in the polyp is shown below.

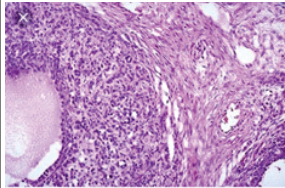
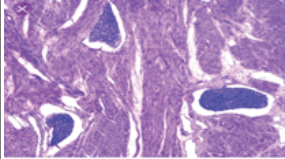
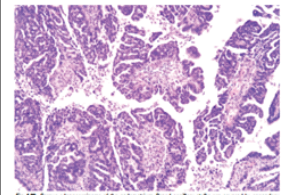
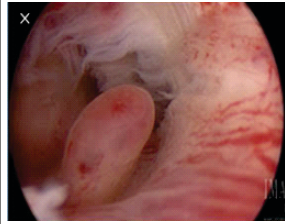
Almost all patients had normal abdomen except two case with 24 weeks mass. Speculum examination showed erosion in 3 cases, one case had hypertrophied cervix, one had cervical growth., one had 3rd degree uv prolapsed. On pelvic examination, 30 cases had bulky uterus, 10 patients had normal uterus and on per rectal examination, most of them had free rectal mucosa and the uterine size was confirmed.

DIFFERENT TYPES OF CARCINOMA ENDOMETRIUM HPE RESULTS IN OUR STUDY:

	NO OF WOMEN(N=44)	PERCENTAGE OF WOMEN
ENDOMETRIOD	35 CASES	80%(9% WAS VILLOGLANDULAR VARIETY
MUCINOUS	3 CASES	6%
SEROUS	5 CESES	12%
CLEAR CELL	NIL	NIL
MISCELLANEOUS	NIL	NIL

EIGHT INTERESTING CASES ALL ASSOCIATED WITH TYPE 2 DIABETES MELLITUS ARE DETAILED BELOW:

1) 55 yrs patient P4L4 ,LCB-24 yrs, married since 35 yrs had postmenopausal bleeding for one month, fractional curettage showed infiltrating villoglandular adenocarcinoma of endometrium, underwent staging laparotomy.	
2) 67 yrs patient, P3L3, LCB-26 yrs, married since 40 yrs, admitted with postmenopausal bleeding with clinically bulky uterus with vaginal metastasis involving bladder base with enlarged inguinal nodes, stage 3A.	Advised Chemoradiation.
3) 62 years patient , P3L3,LCB-32 years with history of PMB had clinically palpable 16 weeks uterus and imaging showed an enlarged uterus 11.2X7.3cm,with altered hypoechoic lesion in endometrium and enlarged ovary. The HPE was infiltrating Endometriod adenocarcinoma of uterus with SECONDARY DEPOSITS IN OVARY. Staging laparotomy& referred for radiotherapy.	
4) 65 years patient ,P5L5, LCB-40 years admitted with postmenopausal bleeding had breast malignancy operated 10 yrs back ,was on TAMOXIFEN for 5 years,underwent staging laparotomy in view of HPE showing infiltrating adenocarcinoma of uterus.	Patient was put on follow up

<p>5)68 yrs patient P2L2 ,LCB- 35 years married since 30 years admitted with third degree uv prolapse and postmenopausal bleeding,clinically bulky uterus with left adnexal mass. On evaluation CECT showed an adnexal mass and enlarged uterus and patient underwent staging laparotomy.HPE came out as infiltrating endometrial adenocarcinoma with ADULT GRANULOSA CELL TUMOUR OF OVARY.(grade2) and patient was referred for chemotherapy.</p>	
<p>6) 35 yrs patient ,with one abortion, NULLIGRAVIDA admitted with profuse menorrhagia with MRI showing ?fibroid polyp in fundus ,hysteroscopic curettage showed LOW GRADE ENDOMETRIAL STROMAL SARCOMA, patient went against medical advice.</p>	
<p>7) 65 yrs patient,P4L4,LCB 30 yrs,married since 40 yrs, admitted with PMB and mass abdomen. On examination patient was emaciated, no supraclavicular nodes,mass abdomen 18x20 cm varying consistency,occupying lower abdomen with bulky uterus,cervix normal, ca 125 was 560.Staging laparotomy done and report turned out to be PAPILLARY SEROUS CARCINOMA OF OVARY WITH ENDOMETRIUM, nodes negative, patient was put on follow up.</p>	
<p>8) 65 years P3L3,LCB 18 yrs with history of post menopausal bleeding, diabetes and hypertension complicating with endometrial mass in usg and hysteroscopy showing a pulsating polyp was planned for staging laparotomy and final HPE came out as ENDOMETRIAL COMPLEX HYPERPLASIA WITH FOCAL AREAS OF ENDOMETRIAL MALIGNANCY IN THE POLY.</p>	

CONCLUSION

1. This study shows a consistent positive association between diabetes and endometrial cancer with almost four times risk exaggerated by **obesity and sedentary habits.**

2. **Hyperinsulinemia** by itself and by causing increased bioactive estrogens and IGF-1 contributes to tumourogenesis.

3. Low levels of adiponectin which is an insulin sensitizer ia also serves as a link between diabetes, hormonal abnormalities and endometrial cancer risk..

4. The association of diabetes and endometrial cancer is very strong followed by hypertension and endometrial cancer. Also hypothyroid status and polycystic ovaries contribute to endometrial cancer risk

by providing a consistent anovulatory environment.

5. It is evident from this study that diabetes may increase risk for endometrial cancer especially when combined with obesity and/or physical inactivity.

6. Proper diet which includes fresh fruits ,vegetables & avoidance of junk food and Interventions to reduce body weight and increase physical activity may have important implications in terms of prevention of endometrial cancer and also prompt and early management of diabetic patients and early detection of cancer endometrium in these patients.

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