IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 16, Issue 12 Ver. IX (Dec. 2017), PP 08-13
www.iosrjournals.org

Study of Effect of Dyslipidemia And Insulin Resistance on Colorectalcancerriskpatients in A Teaching Hospital of India

Purnima Dey Sarkar[1], Poonam Kachhawa[2], Kamal Kachhawa[3], Madhavi Dubey[4], Vivek Sinha[5],

[1] *Department of Biochemistry, Professor, Mahatma Gandhi Memorial Medical College, Indore, India*
[*2] *Department of Biochemistry, Assistant Professor, Saraswathi Institute of Medical Sciences, Hapur, India*
[3] *Department of Biochemistry, Assistant Professor, Mahaveer Institute of Medical Sciences &Research, Bhopal, India*
[4] *Department of Biochemistry, Professor, Saraswathi Institute of Medical Sciences, Hapur, India*
[5] *Department of Biochemistry, Professor, Saraswathi Institute of Medical Sciences, Hapur, India*
***Corresponding Author: Dr Poonam Kachhawa*

Abstract
Background & Objective: *India, according to Indian Council of Medical Research (ICMR,) the annual incidence rates (AARs) for colon cancer and rectal cancer in men are 4.4 and 4.1 per 100000, respectively. The AAR for colon cancer in women is 3.9 per 100000. Some studies have shown that the incidence of CRC is associated with obesity, hyperinsulinemia, and diabetesmellitus. However, studies on the association between CRC anddyslipidemia and insulin resistance produced conflicting results.*
Patients and Methods: *The case-control study was conducted including total 190 subjects. A total of 95 colorectal cancer patients in which 54 (56.8%) males and 41(43.1%) females newly diagnosed with histologically confirmed colorectal carcinoma, under the age of 80 (range 40-80 years). Controls were 95 age matched disease free individuals in which 52 (54.7%) males and 43 (45.2%) females. Mean ± SD in case and control groups and compared using the Unpaired Student's t-test.*
Results: *Data revealed that BMI, total cholesterol, LDL-C, triglycerides, VLDL-C, fasting glucose, serum insulin, HOMA-IR and CEA were significantly differing in between both male and female cases and controls. HDL-C was significantly low (P < 0.001) in only male cases as compare to male control.*
Conclusion: *The present study confirms the association between dyslipidemia, insulin resistance and the prevalence of colorectal cancer.*
Keywords: *Cancer, Colorectal, Dyslipidemia, Insulin, Insulin Resistance*

Date of Submission: 10-12-2017 Date of acceptance: 23-12-2017

I. Introduction

Colorectal cancer (CRC) is the third most common cancerin men and the second most common in women [1]. Almost 60% of cases are encountered in developed countries. The number of CRC-related deaths is estimated to be approximately 608000 worldwide. In India, according to Indian Council of Medical Research (ICMR,) theannual incidence rates (AARs) for colon cancer and rectal cancer in men are 4.4 and 4.1 per 100000,respectively. The AAR for colon cancer in women is 3.9 per 100000 [2]. The vast majority of patients with CRC are above the age of 65 years. CRC occurring before age of forty years accounts for less than 10% of the total CRC [3].Risk factors for CRC can be broadly divided into genetic and environmental or lifestyle-related factors.Lifestyle factors are obesity, increased fat intake, a lack of exercise, alcohol consumption, and smoking.In contrast, consumptionof fiber, vitamin D, and non-steroidal anti-inflammatory drugsreduced the risk of colorectal cancer [4]. Furthermore,an increase in weekly exercise duration, frequency, and intensitywas found to reduce the risk of colorectal cancer [5]. Some studies have shown that theincidence of CRC is associated with obesity,hyperinsulinemia, and diabetic medication use [6]. However,studies on the association between CRCand other factors such as triglyceride andhigh density lipoprotein cholesterol levels have producedconflicting results. Dyslipidemia was defined as a triglyceride (Tg) level ≥ 150 mg/dL, a total cholesterol level ≥ 200 mg/dL, a low-density lipoprotein cholesterol (LDL-C) level ≥ 100 mg/dL, or a high density lipoprotein cholesterol (HDL-C) level < 40 mg/dL for men and < 50 mg/dL for women. Dyslipidemia is a hypothesized risk factor for colorectal adenomas, common neoplastic lesions that can develop into colorectal cancer [7]. Several endoscopy studies of adenomas have investigated, without complete consensus, possible associations with blood concentrations of total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, or triglycerides [8]. In a meta-analysis of studies from the United States, Europe, and Asia, Tian *et al.*reported that

higher levels of LDL cholesterol, triglycerides, and total cholesterol were associated with higher adenoma prevalence, but with differences by geographic region [9].Insulin may influence colorectal carcinogenesis either directly or indirectly through the potent mitogen insulin like growth factor-1 (IGF-1). Hyperinsulinemia enhances the bioactivity of IGF-1 by up-regulating hepatic IGF-1 synthesis, or by reducing hepatic secretion of two IGF binding proteins (IGFBP-1 and IGFBP-2), resulting in higher free or bioactive IGF-1 levels [10]. The insulin and IGF responses are mediated by insulin receptors (IR) and IGF-1 receptors (IGF1R), both of which are widely expressed in normal tissues as well as in epithelial colorectal cancer cells [11]. Binding of insulin or IGF-1 to their receptors is followed by a signal transduction cascade, which may stimulate cell proliferation and suppress apoptosis.The present study sought to examine theassociation between dyslipidemia, insulin resistance and the prevalence of colorectal cancer.

II. Materials And Methods

2.1 Study population

The case-control study was conducted including total 190 subjects.A total of 95colorectal cancer patients in which 54(56.8%)males and 41(43.1%) females, newly diagnosed with histologically confirmed colorectal carcinoma. The age range from 40 to 80 years with a mean age of 61.9± 9.14. Controls were 95 age matched disease free individuals in which 52 (54.7%) males and 43 (45.2%) females with a mean age of 60.0 ± 10.3 years.Study was donebetween, 2013 and 2016 at our institution.

2.2 Specimen and laboratory assays

The subject's age, sex, body mass index (BMI), diabetes status (fasting glucose level ≥ 126 mg/dL), hypertension status, smoking history (nonsmoker or current smoker) and alcohol consumption history (none or current) were considered in the personal history.BMI was calculated as "weight in kilograms divided by height in meters squared (kg/m^2)" with values of 18.5–24.9 kg/m^2 being considered eutrophic, values of 25.0–29.9 kg/m^2 being considered to indicate overweight, and values of ≥30 kg/m^2 to indicate obesity. Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mm Hg and diastolic blood pressure (DBP) ≥ 90 mm Hg or higher. Patients using anti-hypertensive medications were considered to be hypertensive. Blood pressure was measured in the sitting position after a 10-min resting period.About 8ml blood sample was withdrawn from the anticubital vein following overnight fasting. Serum was separated from the clotted blood by centrifugation for 15 minutes at 3000 rpm at room temperature. All serum samples were stored at -80^oC until use. Glucose was measured enzymatically with a glucose oxidase and peroxidase method. Total cholesterol, HDL-C, and triglycerides were also measured enzymatically using commercially available kit of auto analyzer. LDL-C and VLDL-C were calculated by Friedwald's Formula. All biochemical investigations were done by fully automated with automatic analyzer Turbo cam 100 (CPC diagnostics Pvt. Ltd, Alwerpet, Chennai, India). The Serum Insulin (normal value <10 µlU/ml) done by ELISA is a solid phase twosite enzyme immunoassay. It is based on the direct sandwich technique and was estimated by Calbiotech, Inc., Insulin ELISA kit. The CEA (normal value ≤ 3 ng/ml) was estimated by Calbiotech, Inc., CEA ELISA kit. All assays were performed according to the respective manufacturer's instructions. Homeostasis model assessment index (HOMA-IR) to define Insulin resistance, was calculated as: "fasting glucose (mg/dl) × fasting insulin (µlU/ml)/405", the cut-off point was 2.5 or greater. The exclusion criteria included diagnosis of any cancer other than colorectal cancerand they suffering from chronic liver disease, chronic renal disease, heart disease and those taking the medication that influence on blood glucose, serum lipid profile and serum insulin.

2.3 Statistical analysis

Statistical analysis was performed using SPSS 21.0 software. We initially compared baseline characteristics between cases and controls, and also compared by sexes.Results are presented as mean ± SD in case and control groups and compared using the Unpaired Student's t-test. A p value < 0.05 was considered significant.

2.5Ethics statement

The study was approved by the Ethical Committee of the Institute. An informed consent was obtained from each patient.

III. Results

Table 1 showed the baseline characteristics (hypertension, obesity or overweight, diabetes mellitus, smoking and alcoholism) colorectal cancer and control groups. There was higher rate of hypertension and obesity was observed in the colorectal cancer group (41% and 71.6%, respectively; P < 0.001 for both).Fasting blood glucose was higher than 126 mg/dl in 17.8% of cases.With respect to lifestyle habits, smoking and alcohol consumption rates were 38.9% and 31.5% among the colorectal cancer group and 36.8% and 22.1% among the control group respectively (Figure 1a). Table 2 highlights the clinical characteristics of colorectal cancer cases and healthy controls in the study. The mean age of cases was 61.9 years and the controls group was 60.0 years. Data revealed that BMI, systolic blood pressure,diastolic blood pressure,glucose, total cholesterol, triglycerides,

LDL-C, VLDL-C, serum insulin, HOMA-IR, and serum CEA level were significantly higher (P <0.001) in colorectal cancer cases compare than in controls group. HDL-C significantly decreased (P <0.001) in colorectal cancer patients as compared to control group (Figure 2a, 2b & 2c). There was no significant difference in age between cases and controls. Table 3 shows comparison of biochemical parameters between males and females colorectal cancer cases and their respective healthy control. The data indicated BMI, total cholesterol, LDL-C, triglycerides, VLDL-C, fasting glucose, serum insulin, HOMA-IR and CEA were significantly differing in both male and female cases compare than controls. HDL-C was significantly low(P < 0.001) in only male cases as compare to male control.

IV. Discussion

Our case control study aimed to investigate the association of dyslipidemia and insulin resistance to colorectal cancer prevalence. Our study showed that dyslipidemia, which was definedby triglyceride levels ≥ 150 mg/dL or HDL cholesterol levels < 40mg/dL, increased the risk of colorectal cancer.

V. Dyslipidemia

Whether dyslipidemia is associated with colorectal cancerrisk has been debated for decades [12]. It is hypothesizedthat persons with unfavorable lipid profiles may be susceptibleto chronic inflammation in the gut, possibly related tomechanisms involving bile acid malabsorption or butyratesuppression [13], which can create a microenvironmentthat promotes DNA damage, cellular proliferation, and angiogenesis[14]. High circulating cholesterol levels mayalso be related to increased exposure to insulin-like growthfactors and estrogens, which can increase cellular proliferation[8,15,16].Levels of lipoprotein fractions, most prominently HDLcholesterol and triglycerides are correlated, making it difficultto determine which cholesterol component is driving associationswith adenoma in these studies [17]. Persons with adenoma were more likely to have unfavorable cholesterol profiles at the time of colonoscopy than those without adenoma. The most convincing evidenceforanassociationbetweendyslipidemiaandcolorectalneoplasiawasobservedforhypertriglyceridemia [18].

5.1 Insulin resistance

A possible link between insulin metabolism and colorectalcancer has been hypothesized [10], and it is supported by experimentalstudies [19,20]. The epidemiological evidence ismostly indirect, coming from studies linking overweight andobesity (an important determinant of hyperinsulinemia andinsulin resistance) to both colorectal carcinoma and adenomas and studies linking single factors influenced by insulinmetabolismto colon cancer[21-23]. =Insulin may increase the risk of colorectal cancer through a number of mechanisms. Insulinhas been shown to affect growth of normal and neoplasticcolonic epithelial cells and to have mitogenic action in vitro [19], and in experimental animals [20] these actions can take placeeither directly or indirectly through IGF-1. Coloncancer cells have been shown to have both insulin and IGF-1receptors. Insulin, in addition to regulating IGFaction through the effect on the availability of IGF-1 bindingproteins, may bind to IGF-1 receptors [7,10]. Hyperglycemia,a feature of insulin resistance, may affect colorectal cancer riskthrough an inhibition of colonic motility [24].

VI. Conclusion

In conclusion, our findings indicated that the prevalence of dyslipidemia and insulin resistance in colorectal cancer patients is relatively high. Therefore, further analytical and multicentric studies are needed to better understand the role of dyslipidemia and insulin resistance in development of colorectal

Refrences

[1]. GLOBOCAN 2008 (http://globocan.iarc.fr/factsheets/cancers/colorectal.asp) (2008).
[2]. NCRP (2013) Three-year report of the population based cancer registries- 2009-2011. National cancer registry programme, Indian council of medical research (ICMR), Bangalore, India, 2013.
[3]. Zafar SY, Abernethy AP, Abbott DH, *et al*. Comorbidity, age, race and stage at diagnosis in colorectal cancer: a retrospective, parallel analysis of two health systems. BMC Cancer. 2008;8:345.
[4]. Lieberman DA, Prindiville S, Weiss DG, Willett W; VA Cooperative Study Group 380. Risk factors for advanced colonic neoplasia and hyperplastic polyps in asymptomatic individuals. JAMA. 2003;290:2959–67.
[5]. Kim MC, Kim CS, Jeong TH. The effect of physical activity on colorectal polyps. J Korean Acad Fam Med. 2005;26:391–6.
[6]. Kono S, Honjo S, Todoroki I, Nishiwaki M, Hamada H, Nishikawa H, et al. Glucose intolerance and adenomas of the sigmoid colon in Japanese men (Japan). Cancer Causes Control. 1998;9:441–6.
[7]. Giovannucci E. Metabolic syndrome, hyperinsulinemia, and colon cancer: a review. Am J ClinNutr. 2007;86(3):836–842.
[8]. Nishihara R, Wu K, Lochhead P, *et al*. Long-term colorectalcancer incidence and mortality after lower endoscopy. N Engl J Med. 2013;369(12):1095–1105.
[9]. Tian Y, Wang K, Li J, et al. The association between serum lipids and colorectal neoplasm: a systemic review and meta-analysis. Public Health Nutr. 2015;18(18):3355–3370.
[10]. Giovannucci E. Insulin, Insulin-Like Growth Factors and Colon Cancer: A Review of the Evidencel. Jn.nutrition. 2001;1:0022–3166.

[11]. Pollak M. Insulin and insulin-like growth factor signalling in neoplasia. Nat Rev Cancer. 2008;8(12):915–28.
[12]. McKeown-Eyssen G. Epidemiology of colorectal cancer revisited: are serum triglycerides and/or plasma glucose associated with risk? Cancer Epidemiol Biomarkers Prev. 1994;3(8):687–695.
[13]. McMichael AJ, Potter JD. Host factors in carcinogenesis: certain bile-acid metabolic profiles that selectively increase the risk of proximal colon cancer. J Natl Cancer Inst. 1985;75(2):185–191.
[14]. Aleksandrova K, Nimptsch K, Pischon T. Influence of Obesity and Related Metabolic Alterations on Colorectal Cancer Risk. CurrNutr Rep. 2013;2:1–9.
[15]. CoussensLM,Werb Z. Inflammation and cancer. Nature. 2002;420(6917):860–867.
[16]. Potter JD. Hormones and colon cancer. J Natl Cancer Inst. 1995;87(14):1039–1040.
[17]. Davis CE, Gordon D, LaRosa J, *et al*. Correlations of plasma high-density lipoprotein cholesterol levels with other plasma lipid and lipoprotein concentrations. Circulation. 1980;62(4):24–30.
[18]. Passarelli MN, Newcomb PA. Blood Lipid Concentrations and Colorectal Adenomas: A Systematic Review and Meta-Analysis of Colonoscopy Studies in Asia, 2000–2014. Am J Epidemiol. 2016;183(8):691–700.
[19]. Wong M, Holdaway IM. Insulin binding by normal and neoplastic colon tissue. Int J Cancer. 1985;35:335–411.
[20]. Tran TT, Medline A, Bruce WR. Insulin promotion of colon tumors in rats. Cancer Epidemiol. Biomark. Prev. 1996;5:1013–1015.
[21]. Bayerdorffer E, Mannes GA, Ochsenkuhn T, Kopcke W, Wiebecke B, Paumgartner G. Increased risk of "high-risk" colorectal adenomas in overweight men. Gastroenterology. 1993;104:137–144.
[22]. Weiderpass E, Gridley G, Nyren D, Ekbom A, Persson I, Adami HO. Diabetes mellitus and risk of large bowel cancer. J Natl Cancer Inst. 1997;89:660–667.
[23]. Will JC, Galuska DA, Vinicor F, Calle EE. Colorectal cancer: another complication of diabetes mellitus? Am J Epidemiol. 1998;147:816–825.
[24]. Sims MA, Hasler WL, Chey WD, Kim MS, Owyang C. Hyperglycemia inhibits mechanoreceptor-mediated gastrocolonic responses, and colonic peristaltic reflexes in healthy humans. Gastroenterology. 108:350–359.

Table 1:- Baseline Characteristics of Colorectal Cancer Cases and Healthy Controls

Parameters	**Case** **N (%)**	**Control** **N (%)**
Hypertension	39 (41.0%)	29 (30.5%)
Obesity or Overweight	68 (71.6%)	35 (36.9%)
Diabetes mellitus	17 (17.8%)	9 (9.4%)
Smokers	37 (38.9%)	35 (36.8%)
Alcoholics	30 (31.5%)	21 (22.1%)

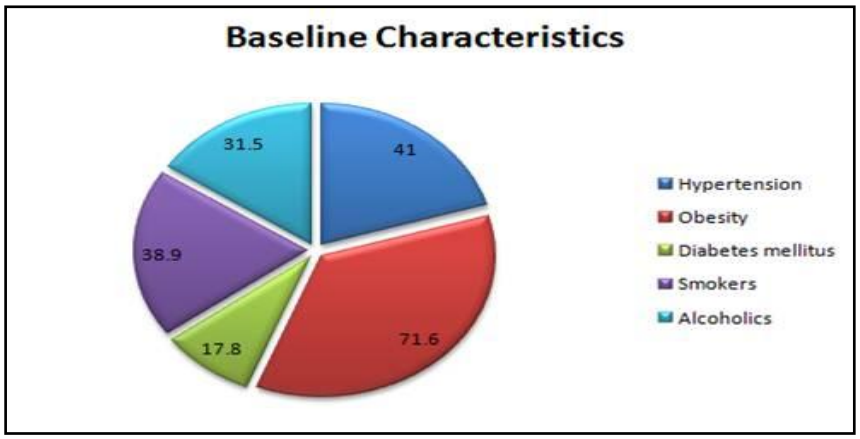

Figure 1a. Baseline characteristics of Colorectal Cancer Cases**.**

Table 2:-Clinical Characteristics of Colorectal Cancer Cases and Healthy Controls**.**

Parameters	**Case** **(n = 95)** **Mean± SD**	**Control** **(n = 95)** **Mean± SD**	***p* value**
Age (year)	61.9 ± 9.14	60.0 ± 10.3	0.20 NS
BMI (kg/m^2)	26.7 ± 2.72	23.7 ± 2.15	<0.05
SBP (mmHg)	138.3 ± 17.9	130.2 ±10.2	<0.05
DBP (mmHg)	87.6 ± 10.3	81.4 ± 7.61	<0.001
Total cholesterol (mg/dl)	212.3± 45.6	171.9± 30.5	<0.001
HDL-cholesterol (mg/dl)	40.4 ± 10.14	44.7 ± 6.92	<0.05
LDL-cholesterol (mg/dl)	139.4 ± 46.8	99.70 ± 27.9	<0.001
Triglycerides (mg/dl)	162.2± 31.7	137.1 ± 36.9	<0.001
VLDL-cholesterol (mg/dl)	32.4 ± 6.35	27.4 ± 7.39	<0.001
Fasting Glucose (mg/dl)	109.0± 14.2	101.4± 11.5	<0.001
Serum Insulin (µlU/ml)	17.57± 5.79	10.28 ± 6.10	<0.001
HOMA-IR	4.87± 2.16	2.69± 1.93	<0.001
CEA (U/ml)	28.28 ± 11.7	2.97± 0.73	<0.001

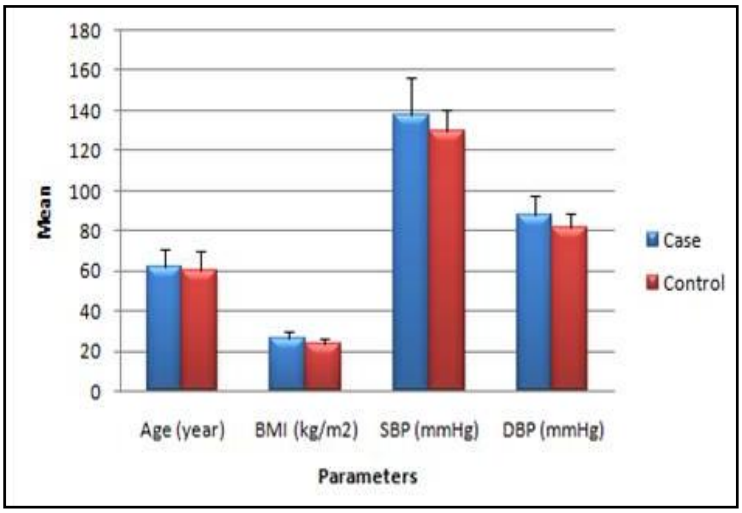

Figure 2a. Physiological parameters of Colorectal Cancer Cases and Healthy Controls

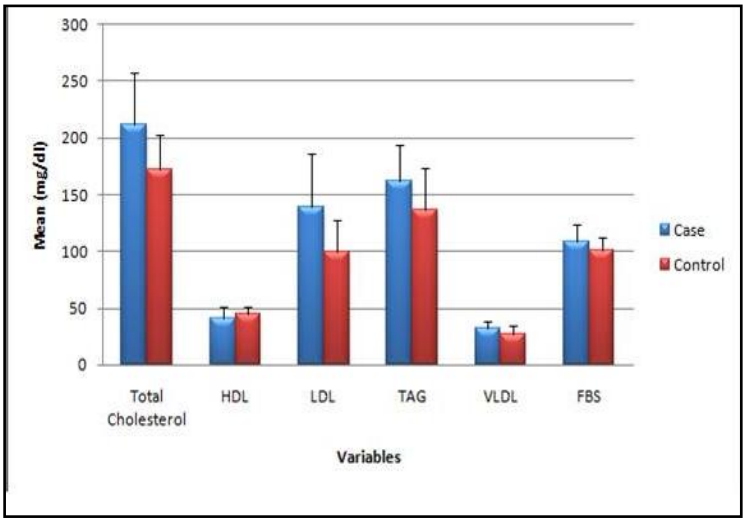

Figure 2b. Lipid Profile of Colorectal Cancer Cases and Healthy Controls

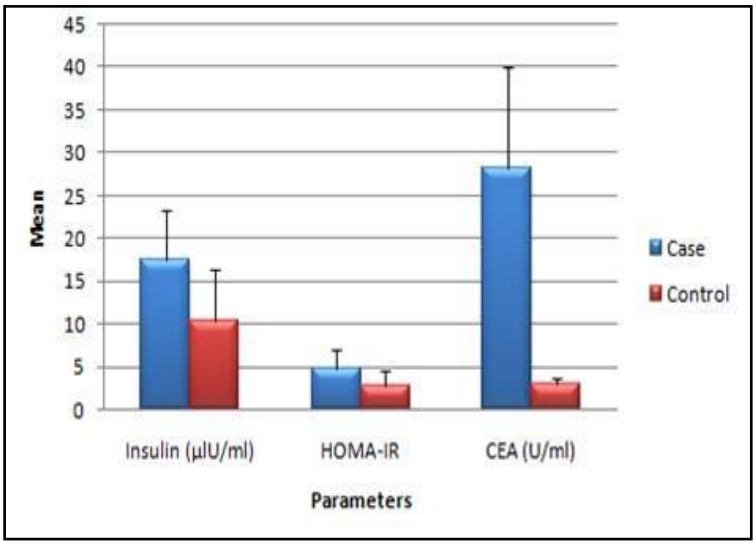

Figure 2c. Insulin, HOMA-IR and CEA of Colorectal Cancer Cases and Healthy Controls

Table 3:- Comparison of Biochemical variables between Male and Female colorectal cancer cases and healthy control

Parameters	**Male**			**Female**		
	Case (n = 54) Mean± SD	**Control (n = 52) Mean± SD**	***p* value**	**Case (n = 41) Mean± SD**	**Control (n = 43) Mean± SD**	***p* value**
Age (year)	62.3 ± 9.49	60.8 ± 10.0	0.44 NS	61.8 ± 8.76	60.9 ± 11.0	0.70 NS
BMI (kg/m^2)	26.0 ± 2.40	23.8 ± 2.22	<0.001	27.6 ± 2.94	23.8 ± 2.09	<0.001
SBP (mmHg)	136.8 ± 15.2	130.4 ±10.5	<0.05	140.5 ± 21.4	129.3 ±10.0	<0.05
DBP (mmHg)	86.2 ± 8.00	81.2 ± 8.36	<0.05	89.6 ± 12.8	81.0 ± 6.45	<0.05
Total cholesterol (mg/dl)	202.9 ± 42.5	173.1 ± 30.4	<0.05	224.3 ± 48.5	170.9 ± 30.1	<0.001
HDL-cholesterol (mg/dl)	36.9 ± 6.92	44.9 ± 6.65	<0.001	45.5 ± 11.5	44.3 ± 7.44	0.52 NS
LDL-cholesterol (mg/dl)	133.0 ± 41.8	100.4 ± 29.3	<0.001	147.6 ± 53.2	99.51 ± 30.6	<0.001
Triglycerides (mg/dl)	164.8 ± 36.7	138.5 ± 45.7	<0.05	155.6 ± 19.3	135.6 ± 22.4	<0.001
VLDL-cholesterol (mg/dl)	32.9 ± 7.35	27.7 ± 9.14	<0.05	31.1 ± 3.86	27.1 ± 4.49	<0.001
Fasting Glucose (mg/dl)	107.1 ± 13.5	101.2 ± 11.8	<0.05	111.7 ± 15.2	101.6 ± 11.6	<0.05
Serum Insulin (µlU/ml)	17.52 ± 5.30	9.58 ± 5.34	<0.001	17.84 ± 6.47	11.31 ± 7.05	<0.001
HOMA-IR	4.75 ± 1.97	2.48 ± 1.68	<0.001	5.09 ± 2.42	2.99 ± 2.26	<0.05
CEA (U/ml)	30.73 ± 12.2	2.96 ± 0.68	<0.001	24.35 ± 10.0	2.98 ± 0.80	<0.001

*Dr Poonam Kachhawa. "Study of Effect of Dyslipidemia And Insulin Resistance on Colorectalcancerriskpatients in A Teaching Hospital of India." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) 16.12 (2017): 08-13