Interrelationship between Insulin Resistance and Nephropathy in Non-Diabetic Chronic HCV Genotype 4 Patients

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Abstract: Data are controversial about different hepatitis C virus (HCV) genotypes in causing insulin resistance (IR) in chronic HCV patients with nephropathy. **Patients and methods:** This study included 40 patients with chronic HCV genotype 4 (group I), 40 patients with chronic HBV (group II), and 20 healthy controls (group III). All subjects were non-diabetic. Group I patients was subdivided into two categories: IA (22 patients without nephropathy), and IB (18 patients with early nephropathy). **Results:** Fasting serum insulin, homeostasis model assessment of insulin resistance (HOMA-IR), homeostasis model assessment of B-cell function (HOMA-B), and TNF-α were significantly higher in group I compared to group II and group III. Estimated glomerular filtration rate (eGFR) was significantly lower in group I compared to groups II and III. Meanwhile, in group I, urinary microalbuminuria (UA) was significantly present in 18 patients (45%), compared to none (0%) in the other two groups ($p=0.001$). Specifically, in group I, fasting serum insulin, HOMA-IR, HOMA-B, and TNF-α were significantly higher in subgroup IB compared to subgroup IA. **Conclusions:** Chronic non-diabetic HCV genotype 4 is suggested to be associated with IR, increased insulin secretion, and increased TNF-α. The presence of HCV nephropathy is hypothesized to have an additive effect on IR, and further increase insulin secretion, and TNF-α. Therefore, increasing insulin sensitivity, and/or decreasing or blocking TNF-α, seems to be a new targets of therapy for patients with HCV nephropathy.

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1. Introduction:

It is estimated that about 150 to 200 million people have been in contact with HCV worldwide, and approximately 85% are chronically infected. The spectrum of severity of liver disease associated with HCV varies widely, as does the rate of progression towards the cirrhotic stage. The latter seems to depend on several cofactors, such as age, sex, level of alcohol consumption, overweight, immune status and co-infections [1,2] . One of these cofactors is type 2 diabetes (T2D), which has been recognized to modify the course of hepatitis C even at the stage of insulin resistance (IR), a condition that precedes the development of T2D [3,4] .

Insulin resistance and compensatory hyperinsulinemia have been associated with hypertension, hyperuricemia, increased levels of serum triglyceride, smaller denser LDL particles, circulating plasminogen activator inhibitor, and decreased levels of HDL [5,6]. Several small clinical studies have noted insulin resistance in nondiabetic patients with mild renal dysfunction [7–9] .However, there are sparse data on the relationship among insulin resistance, compensatory hyperinsulinemia, and the risk of chronic kidney disease (CKD) in nondiabetics.

Microalbuminuria (MA) is defined as subclinical urinary excretion of albumin and it has been shown to predict the progression of renal disease in patients with diabetes as well as the general population. It clusters with the metabolic syndrome and studies have shown a relationship between MA and individual components of the metabolic syndrome (hyperglycemia, insulin resistance, dyslipidemia, abdominal obesity, and hypertension). As patients with hepatitis C are known to have higher prevalence of some components of the metabolic syndrome, one could hypothesize that individuals with hepatitis C may have higher prevalence of MA. Because of the strong association between hepatitis C infection and chronic renal disease, it would be of importance to explore if unselected patients with hepatitis C infection have higher prevalence of MA (early nephropathy) and the insulin resistance is a cause or result of this nephropathy [10] .

HCV infection has been suggested to be associated with insulin resistance (IR), but data are controversial on the role of different HCV genotypes in causing IR. High levels of proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), have been found in HCV-infected patients and,

thereby, they could be involved in the pathogenesis of IR associated with HCV [11] .

Therefore, we assessed IR, insulin secretion, and TNF-α, in patients with chronic HCV genotype 4 with and without nephropathy, compared to patients with chronic HBV and controls.

2. Patients and Methods

A total of 100 non-diabetic consecutive subjects, categorized into three groups, were included in this study. Group I, included 40 patients with chronic hepatitis due to HCV infection, genotype 4. Group II included 40 patients, with chronic hepatitis due to HBV infection. Group III included 20 healthy control subjects. The three groups were matched by age, sex, and BMI. Group I patients were subdivided into two subgroups: IA (22 patients without nephropathy, and IB (18 patients with early nephropathy).

All patients and controls were recruited from patients attending outpatient clinics (or occasionally inpatient) of Internal or Tropical Medicine Departments, Menoufiya University Hospital, Shebin El-Koom. Controls had no history of liver disease. All studied subjects underwent a detailed clinical history and physical examination. An informed consent was obtained from all subjects enrolled in the study. Chronic HBV infection was identified by compatible history, persistently increased serum alanine aminotransferase (ALT) levels, positive hepatitis B surface antigen (HBsAg) and hepatitis Be antigen (HBeAg) qualitative assays [12].

Chronic HCV infection was evidenced by compatible history, persistently increased serum ALT levels, positive serology for anti-HCV (through the detection of HCV antibodies, using third generation ELISA), active virus replication by detection of HCV RNA by PCR in serum [13] .

Exclusion criteria were patients with diabetes mellitus, HCV genotypes other than genotype 4, evidence of cirrhosis, active alcohol consumption, previous treatment with interferon [because interferon can produce a transient increase of IR, followed by a subsequent phase of recovery or even favorable effects on insulin sensitivity in long-term treatment] [14], treatment with corticosteroids or any other medication known to affect glucose tolerance or insulin secretion, the presence of other concomitant diseases (hemochromatosis, chronic pancreatitis, neoplasia, systemic hypertension, schistosomiasis), and history of chronic renal disease (not due to HCV) or dialysis. IR was determined by the homeostasis model assessment (HOMA-IR) according to the formula: HOMA-IR = [fasting glucose (millimoles per liter) x fasting insulin (milliunits per liter)]/22.5. Insulin secretion was calculated as the HOMA-ß cell index according to the equation: HOMA-ß = [fasting insulin (milliunits per liter) x 20]/[fasting glucose (millimoles per liter) – 3.5] [15] . Patients were considered to have IR if HOMA-IR was >2.7. HOMA-IR was suitable for patients with CRF [16]. Both models have been previously validated against clamp measurements.

Laboratory assessment:

1-All parameters of the liver function tests were done on autoanalyzer SYNCHRON CX5 from Beckman.

2-Human TNF-alpha was detected by ELISA, (Abazyme. 85 Pine Grove St. Needham, MA 02494 USA).[17]

3- Microalbuminuria was detected by Cayman's HSA EIA Kit (competitive assay) Cayman Chemical Company, Ann Arbor, Michigan 48108 USA [18] .

4 -Human insulin was detected by ELISA Kit from Calbiotech (Calbiotech Inc., CA, 91978) [19] .

5-Genotyping was performed by reverse transcription PCR with type-specific primers [20] .

6-Three measures of renal insufficiency were examined, namely MA, serum creatinine, and estimated glomerular filtration rate (eGFR) [21] .

MA was considered if urinary albumin levels were between 30-300 mcg per mg creatinine. Significant proteinuria was present if urinary albumin levels greater than 300 mcg per mg creatinine [21] . High levels of serum creatinine were defined as > 1.2 mg/dL for males and > 1.1 mg/dL for females. Chronic kidney disease was defined as a low eGFR with eGFR <60 ml/min per 1.73 m^2 [22] . eGFR was calculated using the abbreviated equation developed by the Modification of Diet in Renal Disease (MDRD) study [20]: eGFR =186.3 x (sCr) - 1.154 x age - 0.203 x (0.742 if female) [23] .

Statistical Analysis

Data input to the computer was done followed by tabulation and analysis. Analysis was done using SPSS-9 (Statistical Package for Social Sciences version 12). We represent the data in arithmetic mean, standard deviation, frequency and percentage. The following tests were used to analysis the results: analysis of variance (ANOVA), least significant difference, Student "t" test, Chi square test and correlation coefficient test. Statistical analysis was done at level of significance of $P \leq 0.05$.

3. Results

There was no significant difference between the three groups as regards demographic data i.e. age, sex, body height, body weight, and BMI (p >0.05) (Table 1).

Table 2 shows that there was no significant difference between the three groups as regards FBG and HbA1c. However, fasting serum insulin, HOMA-IR, HOMA-B, and TNF-α were significantly higher in group I compared to groups II and III (p=0.000). Also, they were significantly higher in group II compared to group III (p =0.000).

Table 3 shows that serum AST, ALT, and bilirubin were significantly higher in groups I and II compared to group III (p=0.001, p =0.000, and p =0.000, respectively). However, there was no significant difference between groups I and II (p >0.05).

In contrast, serum proteins, serum albumin, and prothrombin activity were significantly lower in groups I and II compared to group III (p =0.005, p =0.001, and p =0.000, respectively). However, there was no significant difference between groups I and II (p >0.05).

Regarding renal function tests, blood urea and serum creatinine, were significantly higher in group I, compared to groups II and III (p=0.001, and p=0.000, respectively). However, there was no significant difference between groups II and III (p >0.05). In contrast, eGFR was significantly lower in group I compared to groups II and III (p=0.000). However, there was no significant difference between groups II and III (p>0.05). Meanwhile, in group I, UA was significantly present in 18 patients (45%), compared to none (0%) in the other two groups (p =0.001).

Specifically, in group I, a comparison was done between patients with normal (subgroup IA) and those with early nephropathy (subgroup IB), there was no significant difference between both subgroups as regards FBG and HbA1c. In contrast, fasting serum insulin, HOMA-IR, HOMA-B, and TNF-α were significantly higher in subgroup IB compared with subgroup IA (Table 4).

Table (1): Comparison among the studied groups as regards demographic data

	Group I (n = 40)	Group II (n = 40)	Group III (n = 20)	F-test
Age (years) Mean± SD	43.78±10.03	40.45±7.00	40.70±8.12	P = 0.182 NS
Sex Males Females	27 (67.5%) 13 (32.5%)	24 (60.0%) 16 (40.0%)	13 (65.0%) 7 (35.0%)	X^2 = 0.499 P = 0.779 NS
Body height (cm) Mean± SD	165.53±7.25	166.23±6.73	166.80±7.72	P = 0.795 NS
Body weight (Kg) Mean± SD	74.78±6.99	75.30±6.93	73.50±9.58	P = 0.539 NS
Body mass index (Kg/m^2) Mean± SD	24.72±2.83	25.39±3.42	24.38±2.53	P = 0.268 NS

Group I= Chronic Hepatitis C Group II= Chronic Hepatitis B Group III= Controls NS= Non-significant

Table (2): Comparison among the studied groups as regards fasting blood glucose, fasting insulin, HOMAIR, insulin secretion and TNF-α

	Group I (n = 40)	Group II (n = 40)	Group III (n = 20)	F-test	LSD
FBG (mg/dl) Mean± SD (Range)	91.73±8.11 70-98	89.00±9.38 76-98	90.80±7.91 74-97	F = 1.023 P = 0.363 NS	
HbA1c (%) Mean± SD (Range)	5.2±0.54 4.7-5.5	5.3±0.46 4.6-5.3	5.2±0.34 4.8-5.2	F = 1.025 P = 0.374	
S. insulin (U/L) Mean± SD (Range)	48.70±34.99 5-92	30.97±19.17 7-75	8.35±5.43 3-17	F = 16.812 P = 0.000*	I vs II,III II vs III
HOMA-IR Mean± SD (Range)	10.93±7.94 1.2-22.5	7.71±3.89 1.4-14.7	1.78±1.06 0.7-3.4	F = 17.625 P = 0.000*	I vs II,III II vs III
HOMA-B Mean± SD (Range)	190.96±140.9 14.9-464.0	147.28±89.42 27.2-337.4	31.56±25.44 7.6-77.8	F = 15.052 P = 0.000*	I vs II,III II vs III
TNF-α Mean± SD (Range)	65.83±70.81 5-210	18.25±19.23 1-82	7.45±4.23 2-12	F = 14.854 P = 0.000*	I vs II,III II vs III

FBG=Fasting blood glucose; S. insulin= Serum insulin; HOMA-IR=Homeostasis model assessment of insulin resistance

HOMA-B= Homeostasis model assessment of insulin secretion; TNF-α= Tumor necrosis factor alpha

NS= Non-significant; * = Significant

Table (3): Comparison among the studied groups as regards laboratory investigations

	Group I (n = 40)	Group II (n = 40)	Group III (n = 20)	F-test	LSD
AST (U/L)					
Mean± SD	99.82±42.28	71.23±29.09	32.35±5.58	F = 28.917	I, II vs III
(Range)	48-183	46-147	22-38	P = 0.001*	I vs II
ALT (U/L)					
Mean± SD	110.3±37.43	101.35±35.39	25.30±8.47	F = 48.715	I, II vs III
(Range)	52-167	50-180	14-35	P = 0.000*	I vs II
S. proteins (g/dl)					
Mean± SD	5.19±0.90	5.19±0.62	6.26±0.45	F = 17.625	I, II vs III
(Range)	4-7.1	4-6	5.8-7	P = 0.005*	I vs II
S. albumin (g/dl)					
Mean± SD	3.14±0.72	3.25±0.93	4.12±0.15	F = 17.092	I, II vs III
(Range)	1.5-4.2	1.2-3.9	4-4.4	P = 0.001*	I vs II
S. bilirubin (mg/dl)					
Mean± SD	1.99±0.66	1.69±1.29	0.85±0.14	F = 71.043	I, II vs III
(Range)	1-3.2	1.2-5	0.7-1	P = 0.000*	I vs II
P.A. (%)					
Mean± SD	67.60±10.57	76.33±7.53	92.80±2.95	F = 61.041	I, II vs III
(Range)	46-90	65-86	90-97	P = 0.000*	I vs II
Blood urea (mg/dl)					
Mean± SD	48.78±19.28	33.10±9.66	28.30±5.09	F = 7.399	I, II vs III
(Range)	20-82	21-60	22-36	P = 0.001*	I vs II
S. creatinine (mg/dl)					
Mean± SD	1.95±0.9	1.11±0.18	0.98±0.21	F = 108.7	I vs II,III
(Range)	1.1-2.9	0.93-1.7	0.7-1.3	P = 0.000*	II vs III
eGFR (ml/min/1.73mm^2)					
Mean± SD	42.97±12.57	80.46-13.4	117.53±29.09	F = 129.30	I vs II,III
(Range)	30.6-78.9	62.7-151.3	82.0-168.4	P = 0.000*	II vs III
Urinary MA					
+ve: No. (%)	18 (45%)	0 (0%)	0 (0%)	X^2 = 0.499	
-ve: No. (%)	22 (55%)	40 (100%)	20 (100%)	P = 0.001*	I vs II,III

AST= Aspartate transaminase ALT= Alanine transaminase S.= Serum Hb.= Haemoglobin
eGFR= Estimated glomerular filtration rate; P.A.= Prothrombin activity; MA=Microalbuminuria
+ve= Positive; -ve= Negative; LSD= Least significant difference NS= Non-significant; * = Significant

Table (4): Comparison between patients without nephropathy and those with early nephropathy, in group I patients, as regards FBG, fasting insulin, HOMA-IR, HOMA-B and TNF-α

	Subgroup A (Without nephropathy) (n = 22)	Subgroup B (Early nephropathy) (n = 18)	t-test
FBG (mg/dl) Mean± SD	91.46±8.38	92.13±7.95	P = 0.803 NS
HbA1c (%) Mean± SD	5.1 ± 0.41	5.3 ±0.49	P = 0.815 NS
S. insulin (U/L) Mean± SD	21.92±17.88	78.63±25.97	P = 0.005*
HOMA-IR Mean± SD	4.83±3.72	17.635.90±	P = 0.001*
HOMA-B Mean± SD	85.80±78.13	310.45±109.08	P = 0.005*
TNF--α Mean± SD	22.17±19.32	131.31±69.57	P = 0.005*

FBG= Fasting blood glucose S. insulin= Serum insulin
HOMA-IR= Homeostasis model assessment of insulin resistance
HOMA-B= Homeostasis model assessment of insulin secretion
TNF-α= Tumor necrosis factor alpha NS= Non-significant * = Significant

4. Discussion

Chronic HCV infects approximately 170 million individuals worldwide and is one of the major causes of mortality and morbidity [24] . Egypt has the highest HCV prevalence in the world [25], and HCV genotype 4 in Egypt represents 90% of all HCV cases. The relationship between chronic HCV infection with

different genotypes and IR remains to be firmly established [26] .

We found that patients with HCV infection had significantly higher serum insulin, HOMA-IR, HOMA-B, and TNF-α, compared with those patients with HBV infection. This is in agreement with other previous reports showing higher IR in chronic hepatitis C than in others hepatopathies [27-29] .

Inflammatory cytokines, including TNF-α, are an integral part of inflammation in chronic HCV infection [30] . In chronic HCV infection, active inflammatory process and fibrosis are associated with increased TNF-α production. Increased levels of TNF-α may lead to IR [31] .

Moucari *et al.* [32] found that IR was less frequent in chronic hepatitis B than in matched chronic hepatitis C cases, irrespective of the stage of liver disease. Furthermore, IR was associated with genotypes 1 and 4 and high serum HCV RNA levels. A correlation between HCV RNA levels and HOMA score has been reported by other studies [33-35] especially in genotype 1 [34] . These results are not, however, confirmed by all investigators. **Anty *et al.*** [36] reported that the HOMA scores were comparable in non-3 genotype HCV patients to those of controls (P = NS). Two Japanese studies failed to identify HCV infection as independent predictor of IR [37,38] .

IR has already identified at the early stage of chronic kidney disease, increasing its degrees linearly with the decline in renal function [39] .

There are sparse data on the relationship between IR and CKD in nondiabetic patients. Several small clinical studies have suggested that insulin resistance might be present in kidney disease patients without diabetes [40-42] . **Vareesangthip *et al.*** [40] found that insulin sensitivity was significantly lower and fasting plasma insulin was significantly higher in adult polycystic kidney disease patients compared with age- and sex-matched subjects with normal renal function. **Fliser *et al.*** [41] examined 29 patients with IgA glomerulonephritis, 21 patients with adult polycystic kidney disease in different stages of renal failure, and 16 healthy age-matched controls. Insulin sensitivity was significantly lower and plasma insulin concentration was significantly higher in the kidney disease patients compared with their matched controls. Insulin sensitivity was not significantly different in patients with different underlying causes of renal disease and was similar in renal patients with a GFR within the normal range, mild to moderate renal failure, or advanced renal failure. These data suggest that IR and concomitant hyperinsulinemia are present early in the course of kidney disease, irrespective of underlying cause. **DeFronzo *et al*.** [43] suggest that insulin-mediated glucose uptake by the liver is normal in persons with chronic renal failure, and tissue insensitivity to insulin is the primary cause of insulin resistance in patients with CKD.

In our work, we found that markers of nephropathy and renal function (MA, serum creatinine, and eGFR) were significantly higher in patients with HCV infection, than those with HBV infection. This is in agreement with some previous studies [44-46] , but in contrast to others [47,48] . In line with our results, **Johnson *et al.*** [49] and **Rossi *et al.*** [50] study, observed a significant reduction in proteinuria when patients with HCV infection were treated with interferon-alpha. This discrepancy of the results, might be due several reasons. The HCV genotype, the definition of renal insufficiency, the duration of HCV infection i.e. the longer the duration of HCV was likely to be associated with greater renal impairment [51] , and the presence of active hepatitis C viremia because renal insufficiency may develop on the presence of active viremia [52] . Moreover, the differences in racial or geographical areas. Finally, decreased muscle mass and decreased creatinine production in patients with cirrhosis, can lead to lower serum creatinine levels, and overestimation of eGFR in patients with liver disease, so some cases of HCV with renal impairment may be missed [53,54] .

The mechanisms of the pathogenesis of HCV associated nephropathy mainly included the glomerular deposition of circulating immune complexes containing HCV and anti HCV antibodies [43] .

Intense discussion about the mechanism of the high prevalence of IR in CKD is ongoing. It has been determined through various studies that it is impossible to talk about only one factor that initiates or accelerates IR in CKD. Nevertheless, among cases of IR, decreased renal insulin metabolism and/or clearance [55] , anemia (especially missing out on or delaying treatment of anemia caused by deficiency of erythropoietin with recombinant human erythropoietin [*r*-HuEPO]) [56-59] , increased uremic toxins, exercise intolerance, [60] metabolic acidosis [56,61] secondary hyperparathyroidism, vitamin D deficiency [62] , endothelial dysfunction, oxidative stress [63] ,and microinflammation [63] may be considered.

In our study, IR was significantly higher in patients with early nephropathy and microalbuminuria.

Several epidemiologic studies have reported a positive relationship between IR and the risk of MA in nondiabetic patients [64,65] . In the Insulin Resistance Atherosclerosis Study, **Mykkanen *et al.*** [64] examined the relationship of insulin sensitivity to MA in a cross-sectional study of 982 nondiabetic patients. They reported that decreased levels of insulin sensitivity were related to an increased

prevalence of MA. **Fujikawa *et al.*** [65] examine the relationship between IR and risk of MA in 116 nondiabetic Japanese Americans living in Hawaii. Their study indicated that fasting insulin levels and HOMA-IR were significantly higher in participants who developed MA or proteinuria during follow-up compared with those who did not. They concluded that IR appeared earlier than the appearance of MA.

In our work, TNF-α was found to be significantly increased in patients with HCV with nephropathy, compared to those with normal renal functions. This coincides with other studies [66-69] .

It is well established that TNF-α plays a significant pathophysiological role in different experimental models of renal diseases such as lupus nephritis, crescentic glomerulonephritis, and the remnant kidney model of nephropathy [70,71] . It is important to note that TNF-α may not only be produced in the diabetic kidney by infiltrating macrophages but also intrinsically by renal cells such as endothelial, mesangial, glomerular and tubular epithelial cells [72]. Additionally, the cytotoxic effects of TNF-α can directly induce damage to glomerular, mesangial and epithelial cells [71]. TNF-α also promotes the local generation of superoxide, which affects the barrier function of the glomerular capillary wall resulting in enhanced albumin permeability, independently of diabetic homodynamic effects and inflammatory cytokines activation [73] . TNF-α has stimulatory effects on sodium uptake by proximal tubule cells contributing to sodium retention and renal hypertrophy[74]. The increase in renal TNF-α production in IR/T2D appears to be related to hyperglycemia and formation of AGE products. Diabetic patients had approximately 3-fold higher serum TNF-α than non-diabetic individuals; however, serum TNF-α concentration was increased only in diabetic patients with micro- or macro-albuminuria as well as in subjects with overt nephropathy and renal insufficiency suggesting a significant relationship between serum TNF-α and urinary albumin excretion. [72].

The limitations in our study included the cross sectional design, and the relatively small number of study patients to allow firm conclusions. In addition, we did not obtain cryoglobulin levels for our patients and the lack of histological liver biopsy data.

Conclusions:

HCV infection genotype 4 in non-diabetic patients, is suggested to be associated with IR, increased insulin levels and increased TNF-α. HCV and IR are associated to an extent that cannot be merely explained by chance, which suggests that HCV interferes directly and/or indirectly (by modulating the production of specific cytokines, like TNF-α) with glucose metabolism.

For instance, our findings do not allow one to determine whether insulin resistance and concomitant hyperinsulinemia contribute to the initiation or progression of CKD, whether impaired renal function contributes to the development of insulin resistance, or whether insulin resistance is merely a marker for other causes of CKD in chronic HCV patients. Prospective cohort studies or mechanistic clinical studies may provide a better context for answering these questions.

IR process is possible in CKD even in early stage. Our findings of a positive and significant association among IR, hyperinsulinemia, and kidney disease in nondiabetic patients have both clinical and public health implications. First, it may be beneficial to detect and treat IR and concomitant hyperinsulinemia in HCV nondiabetic patients with CKD. Second, a more aggressive approach to reducing IR in individual patients and in populations would substantially lower the risk of CKD. Many lifestyle modification measures, such as a reduction in dietary fat intake and an increase in physical activity, have been demonstrated to reduce IR. Thus, IR should be explored in all patients with HCV nephropathy, it is certain that preventive and therapeutic interventions will decrease cardiovascular morbidity and mortality.

The relationship between TNF-α and the development and progression of HCV nephropathy is very complex and requires further elucidation. However, it is increasingly becoming clear that TNF-α plays significant roles in this scenario. Early assessment of levels of TNF-α could potentially help with early diagnosis and halting of disease progression to ESRD. Also, a better understanding of the role of TNF-α in the progression of HCV nephropathy should facilitate the development of novel treatment(s) and improvement of current therapeutic strategies. However, it is unlikely that this important task can be relegated to a single marker. Rather, in order to increase the power of predictive strategies, multiple markers will be required to increase the likelihood of early detection of the disease process.

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