

Telomere Length, Aggregates, and Capture in Cirrhosis

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ABSTRACT: **Background:** Shortened telomeres were found in patients with cirrhosis, probably reflecting chronic liver injury, continuous regeneration, and destruction of hepatic nodules.

Objectives: To test whether telomere shortening is a general marker of cirrhosis, independent of disease etiology.

Methods: We evaluated telomere length in patients with cryptogenic cirrhosis (largely a late sequela of steatohepatitis) compared to patients with cirrhosis caused by chronic hepatitis B and C (HBV/HCV). We also evaluated telomere aggregates, a sensitive parameter of telomere dysfunction and genetic instability. We analyzed peripheral lymphocytes from 25 patients with cryptogenic cirrhosis, 15 patients with cirrhosis due to chronic viral hepatitis, and 20 age-matched controls. Telomere length was analyzed using quantitative fluorescence in situ hybridization. Aggregate size was divided into three fusion groups of 2–5, 6–10, and 11–15 telomeres, relative to the size of a single telomere.

Results: Shorter telomere length was found in patients with cirrhosis from all three etiologies (mean 121.3 ± 24.1) compared to controls (mean 63.5 ± 23.5). In contrast, there was significantly more fusion of > 5 telomeres only in the HBV/HCV cirrhosis group compared to healthy controls ($P = 0.023$), but not in the cryptogenic cirrhosis group.

Conclusions: While shortened telomeres in peripheral lymphocytes are a general marker of liver cirrhosis, telomere aggregates may signify a more sensitive genetic instability parameter for the diverse, etiology-based malignant potential of cirrhosis. This finding is in agreement with the well-known higher tendency toward developing hepatocellular carcinoma with cirrhosis caused by chronic hepatitis relative to steatohepatitis.

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Telomeres are specialized nucleoprotein complexes that are located at the ends of chromosomes, protecting them from fusion and degradation during cell mitosis by forming a protective cap. In every cell division, chromosomes lose about 50–100 base pairs (bp) in a process known as the end replication problem, which is caused by the inability of DNA polymerase to fully replicate the extreme ends of chromosomes [1,2]. Consequently, the telomere length of each chromosome shortens as cell division progresses. This replicative shortening of telomeres eventually leads to senescence and finally cellular death. In addition, dysfunctional telomeres may recombine and fuse, initiating random chromosome breakage and increasing chromosome instability and the risk of malignant transformation [1,2].

To maintain chromosomal integrity, telomeric repeats are added to the chromosome via the telomerase enzyme, a specialized reverse transcriptase which is normally active in human germ cells, but not in somatic cells. In addition to telomerase-mediated chromosome healing, chromosomal integrity can also be maintained by another mechanism called telomere capture (TC). TC, first described by Meltzer and colleagues [3] in cancer cells, is a process by which broken chromosomes can acquire new telomeres from normal chromosomes to stabilize by nonreciprocal translocation. Tumors use these mechanisms to bypass this replicative crisis and become immortalized by telomere elongation.

One marker of chromosomal instability, seen in various malignant and pre-malignant conditions, is the tendency to form telomere aggregates (TAs), in contrast to the non-overlapping nature of telomeres in normal nuclei [4]. This process is apparent when a three-dimensional (3D) imaging approach is applied. It signifies not just a transient aberration in the 3D organization of the nucleus, but a true end-to-end fusion [4]. TAs are formed during a breakage-bridge-fusion (BBF) cycle that contributes to deletions, gene amplification, and overall genetic changes that are associated with tumorigenesis [5].

Cirrhosis is the common pathway of a broad variety of hepatotoxic insults, mainly viral, autoimmune, drug and alcohol induced, and fatty infiltration [6]. The clinical heterogeneity among patients with the same risk factors for cirrhosis, and

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the diverse clinical courses among cirrhotic patients, suggests that host factors may play a critical role in disease progression [7]. Telomere shortening is a possible genetic risk factor for cirrhosis. This hypothesis proposes that chronic liver injury induces cycles of regeneration and destruction of hepatocytes, and this high turnover culminates in critical telomere shortening and hepatocyte replicative senescence or death. Hepatocyte senescence is a pro-fibrotic state that activates stellate cells, responsible for fibrosis [8,9]. Wiemann and co-authors [10] demonstrated that telomere shortening was a general marker for cirrhosis regardless of its etiology. Furthermore, telomere shortening and senescence were specifically found in hepatocytes, but not in other cell types of the cirrhotic liver.

Since less is known about telomere attrition in peripheral leukocytes of cirrhotic patients and their significance, the aim of the current study was to evaluate some parameters of the telomere system in their peripheral leukocytes and assess the impact of the etiology of cirrhosis on them.

PATIENTS AND METHODS

STUDY DESIGN

This prospective study was conducted at Meir Medical Center, a tertiary referral center in Israel, in which all patients were followed in the outpatient clinics. Three patient groups were included in the study: cryptogenic cirrhosis (n=25), hepatitis B and C (HBV/HCV) cirrhosis (n=15), and healthy controls (n=20), recruited from the general gastroenterology clinic. The HBV/HCV cirrhosis group included 9 patients with HCV, 5 patients with HBV (including 2 with hepatitis D virus [HDV] co-infection), and 1 patient with concurrent HBV/HCV infection. All patients with HCV and 3 of 5 HBV patients were treated with anti-viral therapy. Exclusion criteria were patients with decompensated cirrhosis, defined by Child–Pugh C; hepatocellular carcinoma, diagnosed by cross-sectional imaging; other known active malignancy; age younger than 18 years; or pregnancy.

Cryptogenic cirrhosis (CC) was mainly defined by characteristic computed tomography (CT) imaging of cirrhosis at the clinical context of accompanying metabolic risk factors and after ruling out other etiologies for cirrhosis. Nine patients (36%) had a liver biopsy, showing a characteristic pathology of nodules separated by fibrotic septa, varied levels of macrovesicular steatosis, and the absence of significant inflammation. Among patients with HBV/HCV cirrhosis, 8 (53%) had a biopsy compatible with the diagnosis and the rest had positive serology with characteristic CT imaging of cirrhosis or stage F3/F4 on fibroscan.

A single blood sample was collected from each subject for the purpose of telomere analysis, performed on peripheral blood lymphocytes. This study was approved by the institutional ethics review board, and all participants provided written informed consent.

LYMPHOCYTE CULTURE

Phytohemagglutinin, 0.2 ml heparin (1000 IU), and 1% antibiotics were added to RPMI 1640 culture medium. After incubation, colchicine (final concentration 0.1 µg/ml) was added to the cultures for 1 hour, followed by hypotonic treatment (0.075 mol/L KCl at 37°C for 15 minutes). The lymphocyte suspensions of the three samples were stored at -4°C.

FLUORESCENCE IN SITU HYBRIDIZATION TECHNIQUE

Fresh slide spreads were incubated for 10 minutes in 2× standard saline citrate at 37°C, followed with fixation in formamide (diluted 1:40 in phosphate buffered saline (PBS) and 0.18 g MgCl₂) for 15 minutes. The slides were washed in PBS for 5 minutes and incubated in pepsin solution (75 g lyophilized pepsin dissolved in 50 ml HCl 0.01N) followed by a wash in PBS for 5 minutes.

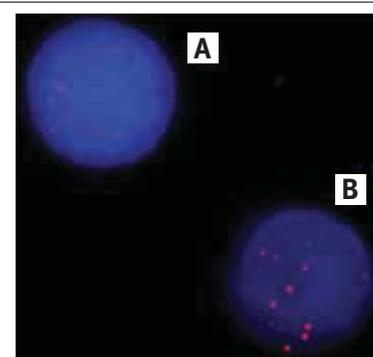
TELOMERE LENGTH AND SIGNAL INTENSITY

Telomere length was quantified as a function of the signal intensity. The cells were categorized as having high (strong) or low (weak) fluorescence after exposing them to the telomere peptide nucleic acid probe. The signal intensity is correlated with long and short telomeres, respectively [Figure 1]. The analysis was conducted for each study group, and the findings were compared. The intensity of fluorescence was subjectively evaluated by an experienced single laboratory worker, who was blinded to the study groups during the workup.

TELOMERE CAPTURE

We used a Cytocell for 15qter (SNRPN, red fluorophore, with 15qter control probe, green fluorophore, cat no: LPU005; Cytocell, Cambridge, UK) and a Cytocell probe for 13qter (13q14.3 red fluorophore, with 13qter control probe, green fluorophore, cat no: LPU006; Cytocell, Cambridge, UK). The analysis was performed primarily on interphase nuclei because most cells were in interphase. In the nuclei, the numbers of the specific loci of the specific chromosome (SNRPN or 13q14.3, orange, the normal disomic loci) and its sub-telomeric region (15qter or 13qter, green) were compared. The number

Figure 1. Assessment of telomere intensity, which is correlated with telomere length, by using fluorescence microscopy for telomere peptide nucleic acid probe. Cells with low [A] and high [B] intensity are shown



of signals of the SNRPN or 13q14.3 locus was compared to the numbers of signals of the sub-telomeric region of the specific chromosome. For example, a normal appearance is two orange and two green signals (2R:2G), while an abnormal appearance, which represents telomere capture, is two orange compared with one (2R:1G), three (2R:3G), or more green signals (the rearranged captured sub-telomeric regions). Approximately 200 nuclei from each sample were analyzed and the slides were scored blindly.

TELOMERE AGGREGATE COUNT

As described in detail by Amiel and colleagues [11], aggregate size was divided into three groups relative to the size of a single telomere: fusion of 2–5 telomeres, fusion of 6–10 telomeres, and fusion of 11–15 telomeres.

We used one filter for three colors, automatic exposure for both images, and 100× magnification on an AX70 Olympus Provis microscope (Olympus Corporation, Tokyo, Japan).

RESULTS

Demographic characteristics, body mass index (BMI), and smoking status of the various research groups are shown in Table 1. None of these parameters were significantly different in the groups, although the BMI was, as expected, higher in CC patients.

Telomere length was quantified as a function of the signal intensity. At the low intensity, correlating with shorter telomeres, there were significantly more telomeres per cell in lymphocytes from both CC (mean 123.3 ± 25.1) and HBV/HCV

cirrhosis (mean 119.5 ± 22.2) patients than from healthy control patients (mean 63.5 ± 23.5, *P* = 0.001).

The TC rate was compared among the groups as the percent of cells with TC in the sub-telomeric regions 15qter and 13qter. As shown in Table 2, the percent of normal cells without capture (2R:2G) was significantly higher in the control group compared with the HBV/HCV cirrhosis and CC groups in both probes (*P* = 0.001). The percent of abnormal cells, featuring capture of either one signal (2R:1G) or 3 signals (2R:3G), was comparably higher in both CC and HBV/HCV cirrhosis groups compared with controls in 15qter and 13qter probes; mainly attributed to 2R:1G capture. No significant difference in TC was observed between the two cirrhosis groups.

To calculate the rate of TAs, we first established the baseline of TA in each case in the control group [Table 3]. These background TAs were related to a virtual overlap of telomeres that could not be distinguished using two-dimensional (2D) microscopy. There was significantly more fusions of > 5 telomeres in the HBV/HCV cirrhosis group compared to healthy controls (*P* = 0.023) when subgroups of aggregates were combined, but not in the CC group.

DISCUSSION

In the present study, we found shortened telomeres in peripheral blood leukocytes of patients with cirrhosis due to chronic viral hepatitis or CC, which is largely caused by the metabolic syndrome. The telomeres were equally shortened in cirrhotic

Table 1. Demographic characteristics of the study groups

	HBV/HCV cirrhosis (n=15)	Cryptogenic cirrhosis (n=25)	Controls (n=20)
Age, years, mean ± SD	56 ± 6.2	59 ± 8.6	61 ± 11.3
Male gender, n (%)	7 (47)	13 (52)	8 (45)
Smoking status, n (%)	4 (26)	5 (20)	6 (30)
Body mass index (kg/cm ²), mean ± SD	26.3 ± 3.2	33.2 ± 2.8	27.1 ± 4.2

HBV = hepatitis B virus, HCV = hepatitis C virus, SD = standard deviation

Table 3. The mean number of cells with telomere aggregates in the study population. Presented as percentage of the number of cells (mean ± standard deviation)

Groups	Number of telomere aggregates			
	2–5	6–10	11–15	Combined
HBV/HCV cirrhosis	4.4 ± 2.8	4.8 ± 1.3	4.5 ± 2.2	13.7 ± 2.9
Cryptogenic cirrhosis	5.8 ± 3.4	1.7 ± 1.5	1.6 ± 1.3	9.1 ± 3.3
Control	4.4 ± 3.5	1.5 ± 1.5	1.5 ± 1.4	7.4 ± 3.4
<i>P</i> value	0.7	0.007*	0.022*	0.023*

*For HBV/HCV cirrhosis vs. control

HBV = hepatitis B virus, HCV = hepatitis C virus

Table 2. The percentage of telomere capture signals from the total number of nuclei in the study population (mean ± standard deviation)

Group	15qter probe				13qter probe			
	2R:2G	2R:1G	2R:3G	Total abnormal	2R:2G	2R:1G	2R:3G	Total abnormal
HBV/HCV cirrhosis	80.5 ± 3.2	14.5 ± 5.1	5.0 ± 2.2	19.5 ± 5.2	85.0 ± 3.4	12.3 ± 3.5	2.7 ± 2.1	15.0 ± 3.8
Cryptogenic cirrhosis	79.5 ± 4.1	11.4 ± 4.3	9.1 ± 3.2	20.5 ± 4.5	85.4 ± 3.2	7.2 ± 4.1	7.4 ± 3.1	14.6 ± 4.4
Control	92.9 ± 3.8	2.4 ± 3.1	4.6 ± 2.2	7.0 ± 3.3	92.4 ± 3.4	3.7 ± 3.6	3.9 ± 2.4	7.6 ± 3.5
<i>P</i> value	0.001*	0.001*	0.2	0.001*	0.03*	0.001**	0.07	0.003*

*For HBV/HVC cirrhosis and cryptogenic cirrhosis vs. control

**For HBV/HVC cirrhosis vs. control

HBV = hepatitis B virus, HCV = hepatitis C virus

patients, compared with healthy controls. These findings are in agreement with those of Wiemann and co-authors [10] who also confirmed that hepatocyte-specific telomere shortening and senescence are general markers of liver cirrhosis, regardless of etiology and patient age. Their study assessed liver biopsy cells from patients with viral, autoimmune, or alcoholic cirrhosis. The current study found telomere shortening in peripheral leukocytes, implying that this indicator can be potentially used as a general marker for liver cirrhosis. In addition, our study also included patients with CC, which is closely related to non-alcoholic fatty liver disease (NAFLD), which is one of the major etiologies of cirrhosis.

We also demonstrated that TC, manifested by cells with capture of one or three signals in the sub-telomeric regions, is also stimulated in cirrhotic patients. This mechanism is one of the suggested ways by which cells with shortened telomeres maintain chromosomal integrity. The primary mechanism for maintaining integrity is increased telomerase activity, which is reflected by telomerase reverse transcriptase, the catalytic subunit of telomerase. This finding was also demonstrated by our group in CC patients [12] and in hepatitis C patients without cirrhosis [13]. Altogether, these findings attest to telomere attrition in cirrhosis with attempted mechanisms to overcome this cellular insult.

The current data supports the telomere hypothesis of cirrhosis, meaning that chronic hepatocyte damage from diverse etiologies and concomitant hepatocyte regeneration cause high turnover and accelerated telomere shortening in hepatocytes [8]. When hepatocytes reach a senescent stage, liver regeneration decreases, but activated stellate cells form fibrotic scar tissue in areas of hepatocyte loss. Kitada et al. [9] were the first to demonstrate the relationship between telomere shortening and cirrhosis. Subsequent studies confirmed that telomere length was inversely correlated with the degree of fibrosis, suggesting that telomere shortening may contribute to and be a marker of cirrhosis [10,11].

In addition to the inherent dysfunction of telomeres in the progression of liver diseases, specifically cirrhosis, there are several other rationales for telomere attrition in cirrhosis. First, accelerated telomere loss has been implicated in other systemic and local fibrotic conditions such as scleroderma [14] and idiopathic pulmonary fibrosis [15]. Cirrhosis is another local fibrotic disease with systemic implications; thus, it is not surprising that it is one of the telomere diseases. Indeed, the telomere syndrome encompasses several hematological, pulmonary, and liver diseases, which rarely coexist. Second, the pre-malignant condition of cirrhosis toward hepatocellular carcinoma can theoretically be associated with telomere dysfunction and repression of telomerase. These changes were demonstrated both in mouse models of HBV-associated hepatocellular carcinoma [16] and in human subjects [17]. Third, the underlying etiology of metabolic disorders (diabetes, obesity, dyslipidemia)

associated with NAFLD [18] and chronic viral hepatitis [8,9] have been shown to cause telomere shortening.

Since leukocyte telomere length is highly correlated with that in cells from other tissues [19], we assumed that patients with cirrhosis display telomere dysfunction in peripheral blood lymphocytes as a surrogate marker for accelerated ageing and genetic instability in their hepatocytes. Telomere shortening in peripheral lymphocytes has been previously demonstrated in cirrhosis from any causes [10], as well as in other studies that demonstrated telomerase mutations in sporadic cirrhosis [20,21]. Alternatively, it may also be that the systemic accumulating oxidative stress induced by the cirrhosis itself or accompanying metabolic derangements, is reflected in the telomeres of the peripheral immune system and induce premature aging of the immune system, similar to what has been described in other systemic inflammatory conditions and autoimmune diseases [22].

The only parameter that differed between patients with HBV/HCV cirrhosis and CC was the amount of telomere aggregates in peripheral blood leukocytes. The formation of TA is independent of telomere length, telomerase activity, and TC [4]. Telomere aggregation is not just a transient aberration in the 3D organization of the nucleus. Dicentric chromosomes can form because some of the aggregates represent fusions. These end-to-end fused chromosomes cannot appropriately separate during cell division, but will first generate anaphase bridges and then break apart, leaving one chromosome too short and the other one with a new section. To heal their broken ends, these new chromosomes will each try to fuse with a new chromosome partner, yielding an ongoing BBF cycle that contributes to the overall genetic changes associated with tumorigenesis [4,5]. In previous studies, telomere aggregation was found to be a sensitive marker of genetic instability and is associated with other markers of genetic instability, like random aneuploidy and asynchronous replication patterns [11,23]. Our current findings regarding higher rates of TA in viral hepatitis cirrhosis, and in light of the apparent correlation between TA formation and malignant potential [7], may signify the well-known higher risk for hepatocellular carcinoma in patients with HCV cirrhosis compared to NASH cirrhosis [24].

Additional telomere and telomerase studies with both long-term follow-up and larger samples, encompassing other etiologies of cirrhosis, are needed to reach more definitive conclusions regarding the prognostic value of telomere length and TA in cirrhosis. It also would be useful if the liver, the target tissue for malignancy, would be directly sampled and examined in addition to blood leukocytes, which only indirectly reflect the genetic changes in the hepatocytes. Furthermore, a search for additional molecular cytogenetic parameters is warranted. Nevertheless, the findings of this study highlight the importance of shortened telomeres in peripheral leukocytes as a general marker of liver cirrhosis. Telomere aggregation may be

a more sensitive genetic instability parameter for the differential malignant potential of cirrhosis and the heterogeneous clinical course of these patients.

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Capsule

Impact of co-morbidities on tumor necrosis factor inhibitor therapy in psoriatic arthritis: a population-based cohort study

Ballegaard and colleagues investigated the impact of co-morbidities on disease activity, treatment response, and persistence with the first-trying tumor necrosis factor inhibitor (TNFi) in population-based cohort study of patients with psoriatic arthritis (PsA). Data on patient characteristics, disease activity, and treatment response and persistence were obtained from the DANBIO registry. Information on co-morbidities according to the Charlson Comorbidity Index (CCI) was obtained through linkage with the Danish National Patient Register. Kaplan–Meier plots and Cox proportional hazard regression analyses were performed. Percentages of patients achieving relevant clinical responses were calculated. The authors identified 1750 patients eligible for analyses. Patients with higher CCI scores had higher disease activity measures at baseline and increased occurrence of depression and/or anxiety. Kaplan–Meier curves showed shorter persistence with

treatment for patients with a CCI score ≥ 2 (log-rank $P < 0.001$) and for patients with depression and/or anxiety ($P = 0.027$) compared to patients without co-morbidities. In multivariate analysis, a CCI score ≥ 2 was associated with reduced TNFi persistence compared with patients without co-morbidities (hazard ratio 1.72, 95% confidence interval 1.26–2.37; $P = 0.001$). A smaller proportion of patients with a CCI score ≥ 2 achieved European League Against Rheumatism (EULAR) good response ($P < 0.001$) and EULAR good-or-moderate response ($P < 0.001$) at 6 months compared with patients without co-morbidities. The presence of co-morbidities was associated with higher baseline disease activity, shorter TNFi persistence, and reduced clinical response rates in a cohort of Danish patients with PsA.

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