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Research article

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Increased Occupational Exposure to Physical Stress in Wild-Type Transthyretin Amyloid Cardiomyopathy – A Potential Disease Promoting Mechanism?

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Abstract

Background
The cause of wild-type transthyretin amyloidosis cardiomyopathy (ATTRwt) remains unknown, with mechanical stress being hypothesized as a potential mechanism. No study has investigated the potential impact of occupational physical exposure on ATTRwt development.

Methods
We enrolled 100 participants, including 50 ATTRwt patients with prior carpal tunnel syndrome surgery (CTS), 25 ATTRwt patients without CTS, and 25 age- and gender-matched stable heart failure patients with reduced ejection fraction (HFrEF) as controls. We evaluated self-reported physical work exposure, Danish occupation classification (DISCO-88), history of orthopedic joint-related disorders beyond CTS surgery, hand volumes, and physical status using the Kansas City Cardiomyopathy Questionnaire.

Results
ATTRwt patients had significantly higher physical work exposure than the HFrEF control group (p<0.001), with a higher prevalence of blue-collar work. Knee or hip joint replacement was more frequent in ATTRwt patients (31; 41%) compared to HFrEF patients (2; 8%). ATTRwt patients exhibited larger hand volumes than the HFrEF control group (dominant hand [DH]: 518±80 mL vs. 421±64 mL, p<0.001).

Conclusion
These findings support the hypothesis that long-standing mechanical stress might play an important role in the development of ATTRwt cardiomyopathy and associated ligament disorders.

Trial registration
The study was approved by the Committee of Scientific Ethics of the Central Denmark Region (project ID: 1-10-72-380-21). Date of registration: 17/03/2022

Keywords: Wild-Type Transthyretin Cardiac Amyloidosis, Heart Failure, Pathogenesis, Ligament Disorders, Occupational Exposure

1. Introduction
Wild type transthyretin (TTR) amyloidosis (ATTRwt) is a progressive infiltrative disease leading to restrictive cardiomyopathy associated with heart failure (HF) development and poor survival [1-3]. ATTRwt is characterized by misfolding and deposition of TTR in the heart but may also infiltrate various ligaments, resulting in carpal tunnel syndrome (CTS), lumbar spinal stenosis (LSS), and spontaneous or low energy trauma tendon ruptures [4-8]. The mechanisms behind the misfolding of the TTR protein leading to fibrillogenesis and subsequent organ affection with amyloid deposition are poorly understood in ATTRwt. The cause of destabilization of the TTR tetramer protein with subsequent misfolding, aggregation of monomers, and amyloid fibril formation has been suggested to be related to biomechanical stress and specific proteolytic enzymes such as plasmin [9]. In vitro studies have shown that plasmin can trigger TTR formation under physiological conditions, and animal studies have demonstrated that plasmin activity increases in

skeletal and heart muscle following physical exposure [9,10]. In addition, an increased release of plasmin following intensive physical activity has been shown in humans, and in a pilot study, vigorous recreational activity was demonstrated to be significantly higher in ATTRwt male patients as compared to matched healthy controls [11-13]. ATTRwt affects predominantly men aged above 65 years and have often a history of CTS surgery in addition to other orthopedic joint related surgical treated disorders and from our clinical experience ATTRwt patients have often had a high degree of physical work exposure [8,14,15]. If high physical activity should be a risk factor involved in the development of ATTRwt, it would be expected that the physical exposure should be of a repetitive and long-standing character.

In order to investigate a potential relationship between ATTRwt and physical work exposure, we assessed the following, in this explorative pilot study: Firstly, the self-reported scale of main physical occupational exposure; secondly, the Danish version of the international classification of occupation (DISCO-88); thirdly, we measured hand volumes and assessed number of previous treated orthopedic joint related disorders beyond CTS surgery. Finally, we assessed quality of life with a focus on physical status in ATTRwt patients as compared to controls defined as age and gender matched heart failure patients with reduced ejection fraction (HFrEF).

2. Methods

2.1 Patient Population and Design

Between September 9th, 2022, and March 6th, 2023, a total of 100 consecutive patients were enrolled in the study. In this period, patients were enrolled prospectively when attending the outpatient clinics for scheduled ambulatory visits. The population consisted of 50 patients with ATTRwt with previous CTS surgery and 25 with ATTRwt without CTS. A control group of 25 age- and gender matched patients with classical recently diagnosed HF with reduced ejection fraction < 40 % (HFrEF) served as controls. Patients with HFrEF were selected and examined immediately after they had completed the HF up-titration being clinical stable on the current guideline recommended HF therapy [16]. The patients with ATTRwt were enrolled in the specialized amyloidosis outpatient clinic. Baseline was defined as the time of enrollment. Blood samples, echocardiography, and physical measurements were performed at baseline.

The diagnosis of ATTRwt cardiomyopathy was established by either endomyocardial biopsy, technetium-99m-labelled 3,3-diphosphono-1,2-propanodicarboxylic acid (99mTc-DPD) scintigraphy, or both in combination. A positive 99mTc-DPD scintigraphy with a Perugini Grade 2 or 3 was noted in 61 patients, whereas eight patients were diagnosed by an amyloid-positive endomyocardial biopsy using Congo red staining with subsequent immunohistochemistry and/or mass spectrometry analysis. For six patients, both scintigraphy and biopsy were used to confirm the ATTRwt diagnosis due to positive immunofixation analysis and/or an abnormal kappa/light chain ratio. The p-kappa/lambda light chain ratio was measured, and spike bands were assessed in serum and urine to confirm the absence of light chain amyloidosis. Genetic testing was performed to exclude variant ATTR in all patients.

The diagnosis of idiopathic CTS was established by an orthopedic specialist, which included electroneurography in addition to clinical testing and subsequent surgery.
All ATTRwt patients were tafamidis naive and were not treated with other disease specific modifying therapies. The National Amyloidosis Centre (NAC) disease stage system was used to categorize patients with ATTRwt [17].

2.2 Physical Exposure

All patients completed a visual analogue scale from 1-10 on the physical demands of their previous main occupation referred to as the strenuous work scale (SWS) [18].
The scores are obtained through self-reported assessments of occupational physical exposure, where patients place a single handwritten mark on a 10-cm line representing a continuum between two endpoints “no physical work exposure” at the left end (0 cm) and the “most imaginable physical exposure” at the right end (10 cm). These centimetre measurements from the starting point reflect the patients' level of work exposure. The values acquired can be employed compare exposure levels among patients.

In addition, patients were interviewed at enrolment about their history of occupational physical exposure, including type of occupation. Occupations were coded into DISCO-88, the Danish version of the International Standard Classification of Occupations 1988 [19]. The DISCO-88 coding defined occupations into groups, defining groups 1 to 5 as a primarily sedentary occupation, while groups 6-9 were physically challenging and strenuous, such as farmers or other “blue-collar” work [18].

2.3 Physical Measurements

Hand volume was measured by the standard water displacement method, using a clinically approved volumeter (Baseline Enterprises, Irvington, NY, USA). Previous measurements of hand size have used hand length and width, we choose to measure hand volume by a three-dimensional volumetric method which is intuitively a more appropriate approach for assessing hand size [20].

2.4 Kansas City Cardiomyopathy Questionnaire

The quality of life (QoL) was assessed in all patients by the Kansas City Cardiomyopathy Questionnaire (KCCQ) which is a 23-item patient-completed questionnaire that assesses health status and health related quality of life (HRQoL) in patients with HF. It is validated for patients with HF with or without preserved ejection fraction. The items assess the ability of patients to perform activities of daily living, frequency and severity of symptoms, the impact of these symptoms, and HRQoL within the last 2 weeks. The assessment yields a score for 6 domains (physical limitation, symptom stability, symptoms, self-efficacy, social limitation, and QoL), two summary scores (Functional Summary and Clinical Summary), as well as an Overall Summary score (OSS). Domain scores are transformed to a 0-100 range [21].

2.5 Echocardiography

A standard transthoracic echocardiography was performed by on a GE Vivid 95, Horten, Norway in accordance with current guidelines [22]. Left ventricular ejection fraction (LVEF) was calculated using Simpson's biplane method. The peak systolic left ventricular global longitudinal strain (LVGLS) magnitude was obtained using automated function imaging from standard two-dimensional cine loops with >55 frames/s. LVGLS was calculated using a 17-segment model at the time in systole when the value peaked. In patients with atrial fibrillation, triplane images for strain calculation were performed. Data analyses were performed using EchoPAC PC SW-Only, Version 203, GE Healthcare, Milwaukee, WI, USA.

2.6 Statistical Consideration

Continuous variables were reported as either mean ± standard deviation for normally distributed data or as median (interquartile range [IQR]) for non-normally distributed data. To evaluate normality, Q-Q plots and histograms were utilized. F-tests were used to compare the variance for data. For normally distributed data, non-paired t-tests were used to compare groups, while the Mann-Whitney U test was used for skewed data. When comparing multiple groups, a one-way analysis of variance (ANOVA) was used. For categorical variables were presented as the number of patients and percentage, and comparisons were made using the chi-square test. The software used for all analyses and figures was STATA (STATA/IC 16, StataCorp LP, College Station, TX, USA) and Graphpad Prism (GraphPad Prism version 9.5.1 for Windows, GraphPad Software, San Diego, California USA).

3. Results

The baseline patient characteristics of the three defined patient groups are outlined in Table 1. Across all groups, baseline clinical characteristics were comparable, except for the presence of aortic valve stenosis, where patients with ATTRwt had a significantly higher prevalence of this condition as compared to the control group (24% vs. 0%, p=0.03). The NAC disease stage was found to be similar between the two groups of patients with ATTRwt (p=0.53).

VARIABLE	HFrEF (n=25)	ATTRwt (n=25)	ATTRwt & CTS (n=50)	P
Age, years	81.5 (4.2)	83.1 (4.7)	82.0 (4.9)	0.52
Male, n (%)	23 (92)	25 (100)	48 (96)	0.35
BMI	24.6 (3.3)	24.8 (2.4)	25.8 (2.9)	0.13
Hypertension, n (%)	15 (60)	14 (55)	27 (55)	0.26
Pacemaker, n (%)	11 (44)	8 (32)	11 (22)	0.17
Atrial fibrillation, n (%)	21 (84)	16 (64)	34 (68)	0.24
Diabetes mellitus, n (%)	24 (6)	3 (12)	11 (22)	0.70
Ischemic heart disease, n (%)	13 (52)	7 (28)	15 (30)	0.15
Aortic stenosis, n (%)	0 (0)	6 (24)	12 (24)	0.03*
NYHA, I/II/III-IV, n (%)	8/15/2 (32/60/8)	7/11/7 (28/44/28)	11/19/20 (22/38/40)	0.16
NAC-disease stage, n (%)	N/A	11/10/4 (44/40/16)	22/19/9 (44/38/18)	0.53
Medication				
Loop diuretics, n (%)	18 (72)	16 (64)	38 (76)	0.55
Equivalent Furosemide diuretics dosage, mg	40 [40-80]	80 [40-80]	60 [40-100]	0.25
Thiazide, n (%)	1 (4)	4 (16)	7 (14)	0.35
Mineralocorticoid receptor antagonist, n (%)	13 (52)	3 (12)	6 (12)	<0.01*
Betablocker, n (%)	23 (92)	9 (36)	19 (36)	<0.01*
Metoprolol dosage, mg	100 [75-200]	50 [50-100]	50 [25-80]	0.01*
ACE-I/ARB, n (%)	21 (84)	12 (48)	18 (36)	<0.01*
Anti-coagulants*, n (%)	10 (40)	15 (60)	32 (64)	0.19

Table 1: Patient characteristics and medication at baseline.

ACE, angiotensin-converting enzyme inhibitor; *Anticoagulation= Non-vitamin K antagonist oral anticoagulant /Warfarin; ARB, angiotensin receptor blockers; ATTRwt, wild-type transthyretin amyloidosis; BMI, body mass index; CTS, Carpal tunnel syndrome; eGFR; estimated glomerular filtration rate; HFrEF; Heart failure with reduced ejection fraction; IVS, intraventricular septum; NAC, national amyloid center; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York heart association functional class.

The pharmacological treatment differed as expected as a significantly higher proportion of patients with HFrEF received mineralocorticoid receptor antagonists compared to those with ATTRwt and the patients with ATTRwt and CTS (52% vs. 12% and 3%, p<0.01), beta blockers (92% vs. 38% and 9%, p<0.01), and angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) (84% vs. 48% and 36%, p<0.01). Patients with HFrEF received a significantly higher average dose of metoprolol compared to all patients with ATTRwt (100 mg vs 50 mg, p=0.01).

3.1 Biomarkers & Echocardiographic Characteristics

NT-proBNP and eGFR were comparable between groups, whereas troponin I (TnI) were significantly elevated in ATTRwt with CTS surgery as compared to HFrEF patients (60 ng/L [32-103] vs 26 [13-39] ng/L, p<0.01). As for echocardiographic parameters, patients with HFrEF and ATTRwt differed significantly with respect to LVEF (39% vs 45%, p=0.02), interventricular septum thickness (11 ± 2 vs 18 ± 3, p<0.01), and posterior wall thickness (10±3 mm vs 17±7 mm, p<0.01). Otherwise, cardiac structure and functional echocardiographic parameters were comparable between groups, as shown in Table 2.

VARIABLE	HFrEF (n=25)	ATTRwt (n=25)	ATTRwt & CTS (n=50)	P
LVEF, %	39 (7.4)	47 (11.9)	45 (10.6)	0.02
LVGLS, %	10.6 (3.0)	10.1 (2.8)	10.2 (3.6)	0.87
IVS, mm	10.9 (2.1)	17.2 (3.9)	17.9 (3.2)	<0.01*
PW, mm	10.0 (2.6)	13.2 (3.7)	16.6 (7.4)	<0.01*
LAVI, mL/m2	40.8 (20.7)	47.6 (21.1)	46.4 (13.3)	0.33
E/A ratio	1.5 [1.0-2.4]	1.5 [0.9-2.6]	1.5 [0.9-2.5]	0.95
E/e'	11 (5.1)	13.9 (4.6)	14 (4.9)	0.23
RAVI, mL/m2	35.1 (16.9)	41.3 (17.6)	38.2 (15.7)	0.47
TAPSE, mm	17.5 (5.7)	173 (4.8)	16.1 (5.8)	0.53
TRPG, mmHg	24.9 (8.6)	27.7 (13.5)	26.6 (12.8)	0.75
Biomarkers				
NT-proBNP, ng/L	1712 [625-3105]	2302 [1084- 5489]	1712 [1036-3825]	0.25
Troponin I, ng/L	26 [13-39]	57 [42-91]	60 [32-103]	<0.01*
eGFR,ml/min/1.73m2	58 (18.6)	62 (20.3)	60 (19.0)	0.15
Creatinine, mmol/L	101[87-141]	109 [82-118]	98 [91-104]	0.69

Table 2: Biomarkers & echocardiographic characteristics

ATTRwt, wild-type transthyretin amyloidosis; CTS, Carpal tunnel syndrome; eGFR; estimated glomerular filtration rate; HFrEF; Heart failure with reduced ejection fraction; IVS, intraventricular septum thickness; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVGLS; left ventricular global longitudinal strain (numerical values); NT-proBNP, N-terminal pro-B-type natriuretic peptide; PW, posterior wall thickness; RAVI, right atrium volume index; TRPG, tricuspid regurgitation pressure gradient.

3.2 Physical Work Exposure Characteristics

A self-reported scale of the degree strenuous physical exposure in the main occupation demonstrated a significantly higher degree of physical exposure in ATTRwt as compared to the age and gender matched HFrEF patients (Figure 1A). The highest reported scale value was reported among ATTRwt patients with previous CTS surgery. Patients with ATTRwt and no CTS had the longest time working in their primary occupation, but it was not statistically significant. (41 ± 15 years vs. 40 ± 12 years for ATTRwt and CTS, p= 0.12, vs. 36 ± 12 years, p=0.15)

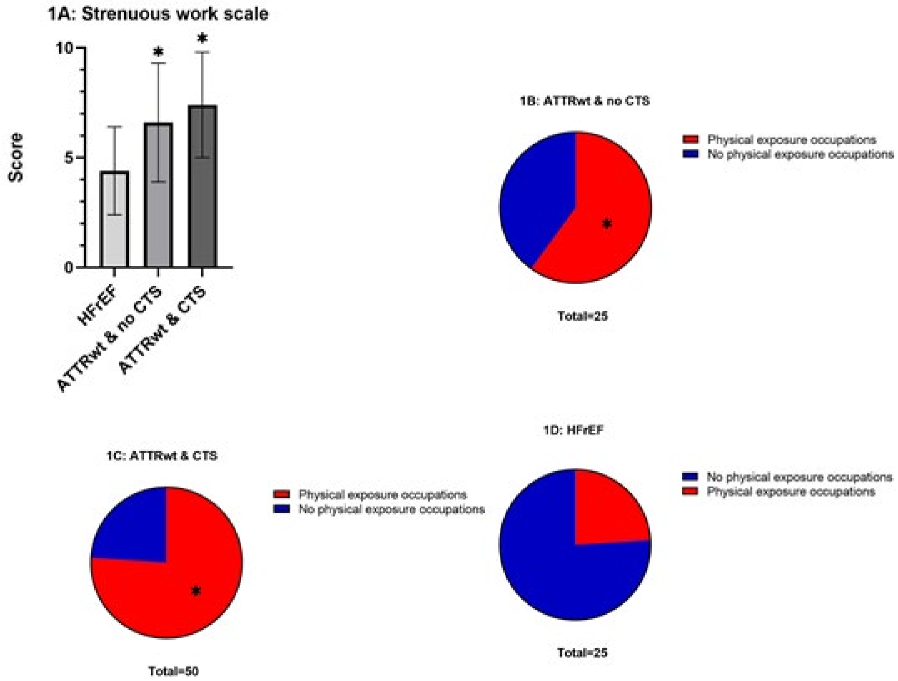

Figure 1: SWS & DISCO-88

1A: Self-reported strenuous work scale score compared between different patient groups.
1B-D: The percentage of patients in the first four classification groups (primarily sedentary occupations) and the last 5 classification groups (primarily increased physical occupations) of the DISCO-88.
* = $p<0.01$ between HFrEF and ATTRwt

ATTRwt, wild-type transthyretin amyloidosis; CTS, Carpal tunnel syndrome; DISCO-88, Denmark standard classification of occupations; HFrEF; Heart failure with reduced ejection fraction; SWS, Strenuous work scale.

The patients were grouped according to the DISCO-88 (figure 1B-D). In patients with ATTRwt and CTS, 38 (76%) patients had occupations classified with increased occupational physical exposure. Occupations with increased physical exposure consisted primarily of farmers, but also craft and trades related occupation and lastly machinery. The remaining twelve (24%) patients had occupations without physical exposure consisting of: Managers, technicians and associate professionals, clerical, services and sales workers. In patients with ATTRwt and no CTS, 15 (60%) had had occupations with increased physical exposure. Finally, in patients with HFrEF only 6 (24%) had had occupations with increased physical exposure. Therefore, demonstrating that individuals with ATTRwt and CTS were significantly more likely to have had occupations with increased physical exposure as compared to HFrEF patients ($p<0.01$). The occupations among subgroups varied greatly, but a notable proportion of all patients with ATTRwt had been working as farmers (23 (30%) vs. 1 (4%) patients, $p=0.01$).

Knee or hip replacement had been performed in 31 (41%) of patients with ATTRwt where 23 (46%) were patients with ATTRwt and CTS, eight (28%) patients with ATTRwt and without CTS, and only two (8%) patients with HFrEF. Surgery of lumbar spinal stenosis (LSS) was performed, in 10 (20%) patients with ATTRwt as eight (16%) patients with ATTRwt and CTS had LSS surgery performed in contrast to two (8%) patients with ATTRwt without CTS had LSS surgery performed. No patients with HFrEF had had LSS surgery. Spontaneous or low-energy trauma tendon ruptures (STR) were noted in twelve (16%) of patients with ATTRwt and CTS, four (16%) patients with ATTRwt without CTS, while one (4%) of patients with HFrEF was noted with STR (Figure 2).

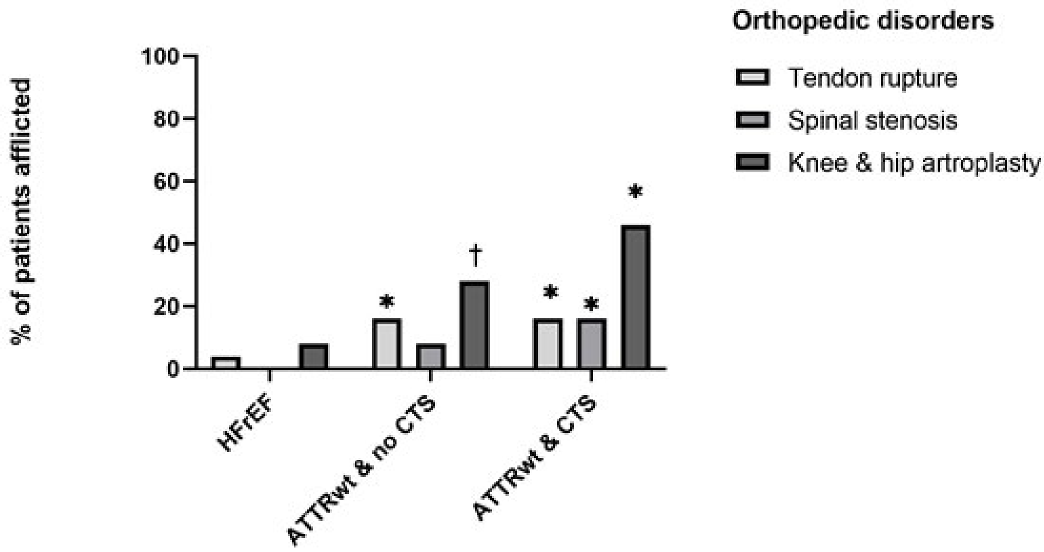

Figure 2: Orthopedic disorders by group

Percentage of how many patients were afflicted by different orthopedic disorders.
* = p<0.01 between HFrEF and ATTRwt and CTS
† = p<0.05 between ATTRwt & CTS and ATTRwt and no CTS

ATTRwt, wild-type transthyretin amyloidosis; CTS, Carpal tunnel syndrome; HFrEF; Heart failure with reduced ejection fraction

3.3 Hand Volumetry and Orthopedic Disorders

Upon examining hand volume, we did not register any difference in the number of individuals with left- or right-hand dominance across all three groups (p=0.43). Patients with ATTRwt had larger hands compared to those with HFrEF, with both the left and right hands being significantly larger (dominant hand (DH), 518±80 mL vs. 421±64 mL, p<0.01) (Figure 3)

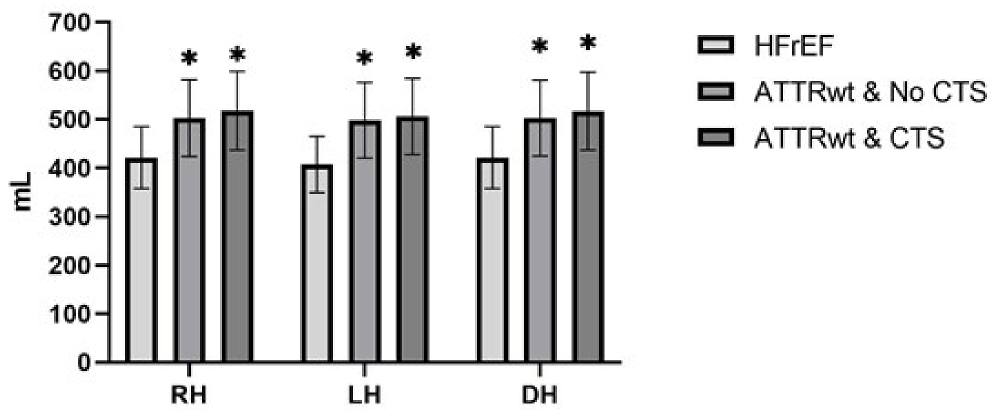

Figure 3: Hand volume of patient's hands

Volume between right, left and dominant hand between the different patient groups.
* = p<0.01 between HFrEF and ATTRwt and CTS
† = p<0.05 between ATTRwt & CTS and ATTRwt and no CTS

ATTRwt, wild-type transthyretin amyloidosis; CTS, Carpal tunnel syndrome; DH, Dominant hand; HFrEF; Heart failure with reduced ejection fraction. LH, Left hand; SWS, Strenuous work scale; RH, Right hand.

3.4 Physical Limitations, Self-Efficacy, and Overall Quality of Life

The ATTRwt with CTS patients reported significantly lower KCCQ scores regarding physical limitation (44.8±21.7 vs. 52.8±18.9, p=0.01) as compared to the HFrEF patients (Figure 4). In addition, the self-efficacy KCCQ score was significantly lower in ATTRwt with CTS patients as compared to HFrEF patients (39.5±26.2 vs. 59.5±13.5, p<0.001) (Figure 4). Significant differences were found in multiple categories of the KCCQ between patients with ATTRwt and CTS and patients with HFrEF. Both overall summary score, and the clinical summary score, differed significantly between ATTRwt patients with CTS and the HFrEF group, respectively (49±19 vs. 61±14.4, p<0.01) and (50±18 vs. 63.2±18, p<0.01) (Figure 4). Although no statistical difference was found between patients with ATTRwt and no CTS and patients with HFrEF, the group with ATTRwt scored lower in all categories as well.

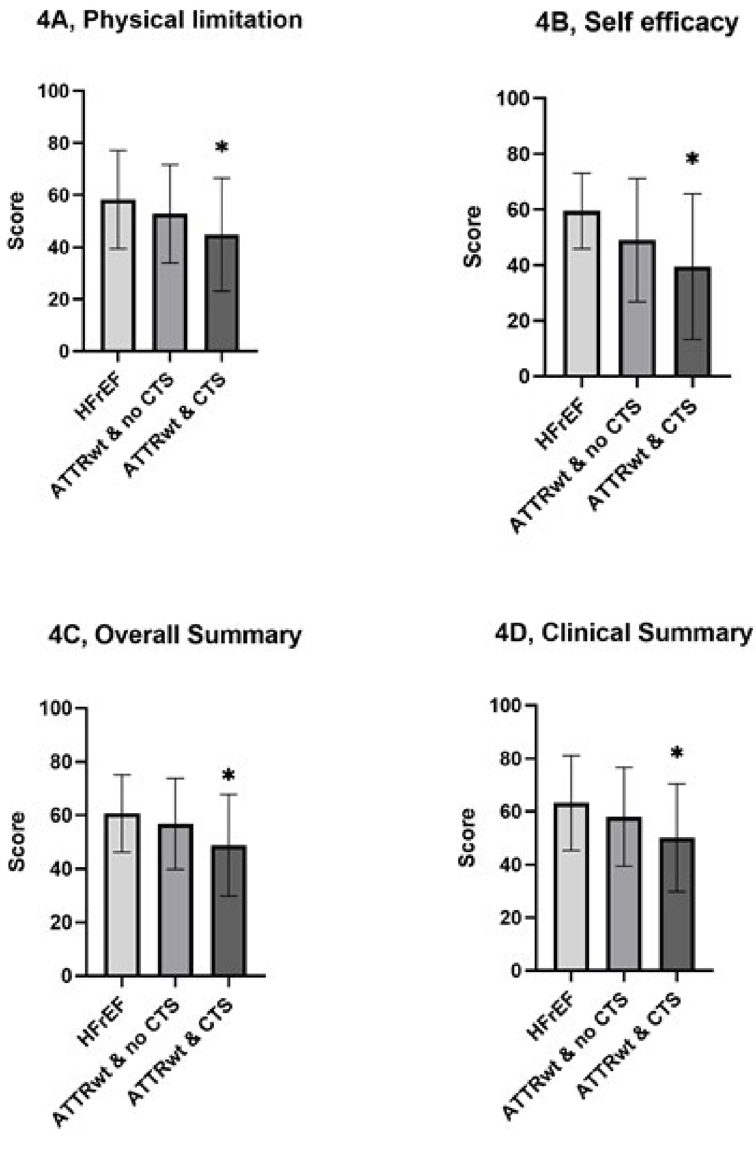

Figure 4: KCCQ domain scores.

4 of the domains of the KCCQ, divided by the three patient groups.
* = p<0.01 between HFrEF and ATTRwt and CTS

ATTRwt, wild-type transthyretin amyloidosis; CTS, Carpal tunnel syndrome;KCCQ, Kansas city cardiomyopathy questionnaire

4. Discussion

The cause of developing ATTRwt with cardiac and ligament organ affection and amyloid deposition are poorly understood. In the present study, we aimed to investigate if increased occupational exposure to physical stress could be related and thereby be a potential factor involved in the development of ATTRwt. The main findings were as follows: Firstly, patients with ATTRwt, and in particular patients with previous CTS surgery, had been exposed to a higher degree of strenuous work, as indicated by a significantly higher self-reported scale of physical workload as compared to HFrEF patients. The prevalence of blue-collar occupation was significantly higher among ATTRwt patients; secondly, a higher prevalence of ligament and joint orthopedic surgery was noted among patients with ATTRwt as compared to the patients with HFrEF; thirdly, we examined the hand volumes and demonstrated that the hand volumes among ATTRwt patients were 25 % larger as compared to controls; finally, the KCCQ assessment of physical limitation and self-efficacy was lower in ATTRwt patients, and particularly in those with previous CTS surgery.

Extra-cardiac manifestations, in particular orthopedic ligament disorders, are reported frequently in ATTRwt patients [7]. CTS in the elderly patients is associated to amyloid deposition in the tenosynovial tissue of the flexor tendons and is the most common reported ligament disorder in ATTRwt [4,23,24]. Reportedly, between 25-66 % of patients with diagnosed ATTRwt have had CTS surgery performed 1-10 years prior to the transthyretin amyloid cardiomyopathy diagnosis [23,25]. In addition, surgery for lumbar spinal stenosis (LSS) has been reported in 14% of the patients at the time of ATTRwt diagnosis, and TTR amyloid infiltration of spine ligaments is frequently demonstrated [4,25]. Furthermore, STR has occurred in approximate 10 % of patients with ATTRwt, and TTR deposits has been demonstrated in ruptured biceps tendon [4,7,26].

Knee and hip joint replacement due to osteoarthrositis has been reported in ATTRwt but the prevalence is largely unknown in the ATTRwt population [8]. In the present study, knee and/or hip atroplasty were performed in 45 % of patients with ATTRwt with CTS, in 28 % of patients of ATTRwt without CTS in contrast to 8% in our control group. TTR amyloid deposition has been demonstrated in ligaments and cartilage from both patients undergoing knee and hip atroplasty, with a higher prevalence with increasing age [27-30]. Histopathology studies have indicated that the amyloid deposition seems not to be related to the osteoartritis itself but is more likely to be an age-related phenomenon, a characteristic similar to what is noted in ATTRwt cardiomyopathy [31]. Mechanical stress following repetitive and long-standing strenuous physical workload has been suggested as a potential cause of TTR destabilization and amyloid deposition in ligaments, joints, and heart [9]. In our study, ATTRwt patients were demonstrated to have had a higher degree of physical work exposure, as indicated by a significantly higher self-reported physical occupation exposure score and a significantly increased number of patients classified as having blue-collar occupation as compared to the HFrEF control group. The high prevalence of ortopedic surgery involving the knee, hip, spine, and tendons among ATTRwt and especially in those with previous CTS surgery indicates that these ATTRwt patients are likely to have been exposed to an increased work load. Even though no data, to the best of our knowledge, is available on the association between hand size and physical work exposure, we measured hand volumes as an intutive indicator for manual strenous long-standing work. Hand volumes were significantly larger among ATTRwt patients, with an increase of 25 % as compared to the HFrEF patients. No previous study has to our knowledge have investigated the association physical work exposure and hand size. Intuitively there would be expected a significant association and from a clinical experience and observation that patients with increased physical occupational exposure often have enlarged hand size. Increased hand volumes might be present as a consequence of physical exposure, with increased volumes of hand and fingers muscles following increased bone mass and thicker tendon tissue. However, tissue amyloid infiltration might also contribute to the enlargement which must be clarified by future studies. The QoL was assessed with a focus on the physical limitation and self-efficacy, showed that the scores were lowest among ATTRwt patients with CTS indicating poorer physical mobility and performance. These findings might be related to the higher prevalence of orthopedic surgically treated disorders in these patients. The higher frequency of joint disorders is likely to be related to the increased physical occupational exposure in addition to frequent amyloid deposition in joints with development of joint dysfunction.

The LV systolic and diastolic performance were comparable between patients with ATTRwt with and without CTS, except for a minor difference in LV posterior wall thickness. This in accordance with recent published data demonstrating comparable cardiac structural and functional parameters in ATTRwt patients with or without ligament disorders [7].

The cause of why TTR are deposited in the heart, ligaments, and joints is still unknown in ATTRwt patients, but the hypothesis that physical induced mechanical stress can destabilize the misfolded TTR into fragment TTR with the development of amyloid fibrils and organ deposition is a potential mechanism. Long-standing and repetitive hard physical work might promote a higher risk of amyloid fibril deposition due to an increased susceptibility of the active joints, and ligaments. Similar, the myocardial workload increases as a consequence of higher cardiac demand during during physical strenuous work which might facilitate amyloid deposition. Plasminogen and plasmin seem to increase during strenuous work, and animal studies have demonstrated that plasmin activity increases in skeletal and heart muscle following physical exposure [9,10]. In vitro studies have shown that plasmin can trigger WT-TTR formation under physiological conditions [9]. Solid scientific prospective documentation on the linkage between the production of TTR-fragments and organ TTR amyloid fibril deposition induced by physical exposure in humans seems difficult to obtain. However, our data shows that ATTRwt have a different physical work exposure profile, have more treated ortopedic disorders, and have anatomically larger hands as compared to age and gender matched HF patients. These findings might indicate that enhanced physical work exposure might be an important factor involved in the development of ATTRwt cardiomyopathy and associated ligament disorders however, larger population-based studies are needed to confirm the present observations.

Some limitations must be taken into consideration. The data on patient main occupational is in nature retrospective but we provide a reasonable estimate of the duration of the main occupation. However, uncertainties about shift to intermediate lesser physical occupations are a limiting factor as well as we do not have any data on patient recreational physical activity levels. However, data on the actual physical hand volumetry, DISCO-88 evaluation and the prevalence of joint and ligament disease are measurable demonstrating a significant difference between groups. The control group consisting of classical recently diagnosed stable HFrEF patients might be considered as a limitation and less optimal control group. However, in contrast to the choice of a control group consisting of HFpEF patients, the aetiology of HFrEF is often more well characterized, homogenous and our ATTRwt population consists of an equal distribution of patients with left ventricular ejection fraction above and below 50 %. Supportive of our choice of control group, the baseline demographics regarding the prevalence of diabetes, body mass index, hypertension, atrial fibrillation, NYHA class were comparable between groups which probably would not have been the situation with a HFpEF control group. We did not have imaging of potential TTR-amyloid deposition of the hands, which could have been of interest with regard to hand volumes and strength. We included mostly males in the study, which is a limitation however, males account for usually 85-90 % of the ATTRwt population, which indicates that the present patient characteristics are a reasonable representative cohort of ATTRwt patients.

5. Conclusion

Increased physical work exposure, a higher prevalence of surgically treated orthopedic joint and ligament disorders, and larger hand volumes were demonstrated in ATTRwt patients as compared to age and gender matched HFrEF patients. These findings support the hypothesis that long-standing mechanical stress might play an important role in the development of ATTRwt cardiomyopathy and associated ligament disorders.

Declarations

Ethics approval and consent to participate

The study was approved by the Committee of Scientific Ethics of the Central Denmark Region (project ID: 1-10-72-380-21). Registration date: 17/03/2022. The study was registered with clinicaltrials.org (ID: NCT05896904). Written informed consent was obtained from all participants, and the study was conducted in adherence to the Helsinki Declaration principles.

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Disclosures

The authors declare that there is no conflict of interest.

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