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Original Article

Comparison of acquired and lifelong premature ejaculation and predictive values of acquired premature ejaculation in clinical presentation: A clinical study

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Abstract

Aim: Premature ejaculation is the most common form of male sexual disease observed clinically. In spite of this, the etiologic factors and disease pathophysiology are still not fully understood. This study compares the most frequently observed premature ejaculation forms to investigate the effective predictive factors in the occurrence of this disease.

Materials and Methods: The clinical records of a total of 109 patients were retrospectively investigated for two types of premature ejaculation with 64 patients in the lifelong group and 42 patients in the acquired group. The study included demographic data like age, marital status and body mass index (BMI), parameters like metabolic syndrome (metS) components according to the cholesterol study group of blood triglycerides, high density (HDL) cholesterol, and fasting blood sugar and measured testosterone. Additionally, the internationally ejaculation latent time(IELT), premature ejaculation- diagnostic tool (PE-DT), internationally prostate symptom score (IPSS), internationally index of erectile function (IIEF) and premature ejaculation (PE)anxiety scoring forms were included in the study.

Results: Among demographic data, there were statistical differences between the ages in the groups (30.6±7.7 vs 44.4±10.1, respectively, p <0.001). Additionally, fasting blood sugar (FBS), triglyceride, HDL cholesterol and testosterone values were statistically different between the groups (p<0.001) and these values were worse in the acquired PE group. Hypertension rates were higher in the acquired PE group compared to the lifelong PE group (9 (21.4%) vs 5 (7.8%), p<0.001). The IIEF score was lower in the acquired PE group (p<0.001). Logistic regression analysis found age and FBS were independent predictive factors [Odds ratio (ODs); 1.144 and 1.044, respectively]. ROC analysis found the cut-off points and AUC values for age and FBS were 36.5 yearsand0.856 and 102.5 gr/dl and 0.746, respectively.

Conclusion: The association of metS components, LUTS and acquired PE was constant. In light of these findings, different from lifelong PE, there is benefit to orienting toward the causes of this disease primarily for treatment of acquired PE.

Keywords: Diabetes mellitus; erectile dysfunction; metabolic syndrome; premature ejaculation; prostate; testosterone

INTRODUCTION

Ejaculation is a mechanical and multifunctional process including contraction of the ductus deferens and opening of the ductus deferens with the sympathetic neuronal system. Early triggering of the neuronal pathways affecting the completion of ejaculation or inhibition of the mechanisms suppressing ejaculation cause premature ejaculation.

Though there are different figures in population epidemiologic studies about premature ejaculation, nearly 15-20% of men experience premature ejaculation complaints in the population. At the same time, premature ejaculation represents the majority of attendances at hospital due to sexual problems. This situation causes anxiety in men. The partners of these men are known to experience emotional and sexual problems due to inability to reach sexual satisfaction (1).

The etiopathogenesis differs due to the types of PE, too. The speculations about serotonin are known to be related with the lifelong PE. On the other hand, psychological or organic factors are more likely to be related with acquired PE (2).

After the two "International Society for Sexual Medicine (ISSM)" meetings in 2007 and 2013, two definitions for lifelong premature ejaculation (PE)and acquired PE are assessed. The definitions are as follows:

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(i) If ejaculation from the first sexual experience always or nearly always occurs in less than 1 minute it is lifelong PE or if the latency duration is about 3 minutes or less with clinically pronounced reduction it is acquired PE, and

(ii) Vaginal entry is always or nearly always insufficient to delay ejaculation, and

(iii) There are negative personal results like distress, frustration and/or avoiding sexual intimacy (evidence level: LOE1a) (3).

Lifelong PE is observed more than acquired PE. Acquired PE is generally observed more in patients with advanced age and more comorbid problems related to advanced age. Patients with acquired PE are those who did not have premature ejaculation compliant in previous sexual experiences and whose premature ejaculation complaint began later. As in the ISSM definition, the ejaculation time in these patients is longer than in the lifelong PE group. Apart from the definitions, another situation that separates the two groups is that, different to lifelong PE, some comorbid diseases and their etiopathogenesis are blamed for acquired PE (e.g., LUTS, prostatism, hyperthyroidism, hypogonadism, etc.) but there is still no evidence-based data about this topic (4).

In our study, we assessed the demographic data, metS components, testosterone measurements and sexual health and lower urinary system questionnaire results of lifelong and acquired PE patients treated in our clinic to assess patients from both PE branches and to observe predictive factors in the etiopathogenesis.

MATERIALS and METHODS

This study was carried out in accordance with the ethical standards of the human experiment (institutional and national) responsible committee and the Helsinki Declaration and with the approval of the ethics committee (M.H.U Istanbul Training and Research Hospital Clinical Research Ethics Committee, Decision no; 2455, Date; 22.06.2020).Patients applying to our clinic from January 2016-December 2018 with premature ejaculation complaints were retrospectively assessed. In total, records from 159 patients were assessed, and 106 patients with full data were included in the study (64 in the lifelong PE group and 42 in the acquired PE group). Patients with variable PE and premature-like or subjective ejaculatory dysfunction patients, hyperthyroidism, psychological disorder, previous prostate surgery, using serotonin reuptake inhibitors (SSRI), testosterone, alpha blockers, 5-alpha reductase inhibitor and phosphodiesterase inhibitor were not included in the study. Apart from this, patients with premature ejaculation complaints were included in the study.

The study included demographic data like age, marital status and BMI, parameters accepted as metS components by the cholesterol study group of blood triglycerides, HDL cholesterol and fasting blood sugar (FBS) and testosterone were measured. Additionally, validated questionnaire forms of the intravaginal ejaculation latent time (IELT), PE diagnostic tool (PE-DT), international prostate symptom score (IPSS) and index of international erection function (IIEF) and the non-validated PE anxiety scoring form were included in the study.

Measurement and Parameter Identification

Routine laboratory and hormonal tests were taken while fasting between 08:00 and 09:00. The metS parameters included in the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) of BMI (≥25 mg/kg), blood pressure (≥130/85 mmHg abnormal or daily antihypertensive medication use), fasting blood sugar(>110 mg/dL or use of oral antidiabetics and/or insulin), triglyceride (≥150 mg/dL) and high density lipoprotein cholesterol (≤ 40 mg/dL) were measured. Testosterone ≤ 3.5 ng/mL was assessed as hypogonadism.

For premature ejaculation duration, patients were questioned about IELT. This questioning classified patients with ejaculation in <1 min as lifelong PE and those with ejaculation in < 3 min as acquired PE.

To identify lower urinary tract complaints of patients, the IPSS questionnaire was used. The IPSS comprises 8 questions and a total of 35 points (0-7 mild, 8-19 moderate and 20-35 severe). The IIEF questionnaire was completed for sexual functions. The IIEF is a multidimensional questionnaire about male sexual function and assesses erectile dysfunction, orgasm function, libido, sexual and overall satisfaction (OS). It comprises 15 questions giving a total of 75 points. The PE-diagnostic tool includes a total of 5 questions, with 3 explaining the ejaculation status, and 2 about the anxiety created in the patient by premature ejaculation with total points of 20 (total score > 11 is accepted as premature ejaculation). Additionally, we completed non-validated PE anxiety scoring by asking the question "How much anxiety have you felt about ejaculation during sexual relations in the last month?" (1: excessive, 2: a lot, 3: moderate, 4: a little and 5: none). Some patients were called by telephone while some completed the forms in the clinic.

Statistical Analysis

For statistical analysis, SPSS 22.0 (IBM Co,Armonk, NY,USA) was used. Continuous variables are given as mean ± standard deviation, while categorical variables are given as frequency distribution and percentages (%). Comparison of continuous variables between groups (age, BMI, FBS, TG, HDL cholesterol, testosterone, PE-diagnostic tool, IIEF, IPSS, premature ejaculation anxiety score, duration of medication use) used the independent t test. With the aim of testing the distribution of group factors for categoric variables (marital status, hypertension), the chi-square test was used. Risk factors affecting acquired PE were assessed with multivariate logistic regression analysis and results are given as Odds ratio (ORs) and 95% confidence intervals. Variables found significant in the multivariate model had receiver operating curve (ROC)

analysis performed and the area under the curve (AUC) and 95% confidence intervals are given with sensitivity and specificity calculations for diagnostic performance. Variables found to be significant in terms of area under the curve had cut-off points calculated according to the Youden index.

RESULTS

There were 64 patients in the lifelong PE group and 42 patients in the acquired PE group. The groups were statistically different in terms of age (30.6±7.7 vs 44.4 ± 10.1 years, respectively, P < 0.001) among demographic data. BMI (26.1± 4.4 vs 27.0± 5.1, P= 0.382) and marital status (yes, 72% vs 81%, P= 0.293) were not different between the groups. FBS, triglycerides, HDL cholesterol, and testosterone values were statistically different between the groups (p < 0.001) and these values were worse in the acquired PE group. As predicted before the study, the rate of patients with hypertension was higher in the acquired PE group compared to the lifelong PE group (9(21.4%) vs 5 (7.8%), respectively, p < 0.001).

Table 1. Demografic and Study data's

	Lifelong PE	Acquired PE	P
Patient (no)	64	42	
Age (year),mean±sd	30.6± 7.7	44.4± 10.1	**<0.001**
BMİ (kg/ m²),mean±sd	26.1± 4.4	27.0± 5.1	0.382
Marriage status (no,%)			0.293
Yes	46 (%72)	34 (%81)	
No	18 (%28)	8 (%19)	
FBS (mg/dl),mean±sd	94.7 ± 17.3	107.9 ± 29.0	**< 0.001**
Triglycerid (mg/dl),mean±sd	94.3 ± 31.9	134 ± 44.5	**< 0.001**
HDL Cholesterol (mg/dl), mean±sd	54.6 ± 20.4	45.0 ± 9.2	**< 0.001**
Testosterone (ng/ml), mean±sd	5.2 ± 1.1	4.2 ± 0.7	**< 0.001**
Hypertension(no,%)	5 (%7.8)	9 (%21.4)	**< 0.001**
PE-DT, mean±sd	15.8 ± 2.4	16.0 ± 2.7	0.246
IPSS,mean±sd	5.2 ± 2.9	8.7 ± 6.3	**<0.001**
İİEF,mean±sd	61.3±13.3	38.3 ± 20,4	**<0.001**
İİEF Orgasmic function score, mean±sd	8.2±6.4	7.5±8.2	0.410
PE anxiety score,mean±sd	1.4 ± 0.6	1.6 ± 0.8	0.061
Medication usage time (month),mean±sd	2.8 ± 2.0	2.8 ± 2.0	0.912
İELT	<1	<3 ve 1-3	**<0.001**

BMİ; Body Mass Index, FBS; Fasting Blood Sugar, HDL; High Density Lipoprotein, PE-DT; Remature Ejaculation Diagnostic Tool, IPSS; International Prostate Symptom Score, İİEF; International Index of Erectile Function, İELT; Intravajinal Ejaculation Latent Time, sd; Standart Deviation

A score of 11 and above on the PE-diagnostic tool is significant for ejaculation. In both our groups the PE-DT score was 11 and above with no differences between the groups (15.8±2.4 vs 16.0±2.7, P=0.246). The IELT was used on the question form to classify PE patients. It was reported as <1 min for all patients in the lifelong PE group and as <3 and 1-3 min for all patients in the acquired PE group. Again, as expected, when patients completed the IIEF to inform patients about the main erection problems, the acquired PE group had lower scores (p<0.001).There was no difference between the groups according to the IIEF orgasmic function questionnaire (questions 9 and 10).The results for the IPSS used to question lower urinary tract complaints, which we suspect are associated with premature ejaculation, were again worse in the acquired PE group (p < 0.001). The premature ejaculation anxiety questioning and medication durations were similar between the two groups (Table 1).

Multivariate (binary) logistic regression analysis was performed to research effective predictive factors for acquired PE. Age and FBS were found to be predictive factors (Odds ratio 1.144 and 1.044) (Table 2).With the increasing of age and FBS parameter, having acquired PE increases 1.14 and 1.04 -fold when compared to having lifelong PE status, respectively.

Table 2. Binary logistics regression analysis of acquired PE

		%95 CI		P
Odds ratio		Lower	Upper	
Age	1.144	1.008	1.298	**0.038**
FBS	1.044	1.003	1.086	**0.033**
Triglyserid	1.011	0.990	1.032	0.308
HDL	0.994	0.964	1.025	0.704
Testosterone	0.520	0.229	1.178	0.117
Hypertension	0.295	0.028	3.071	0.307
İPSS	1.051	0.863	1.279	0.620
İİEF	0.992	0.943	1.044	0.767

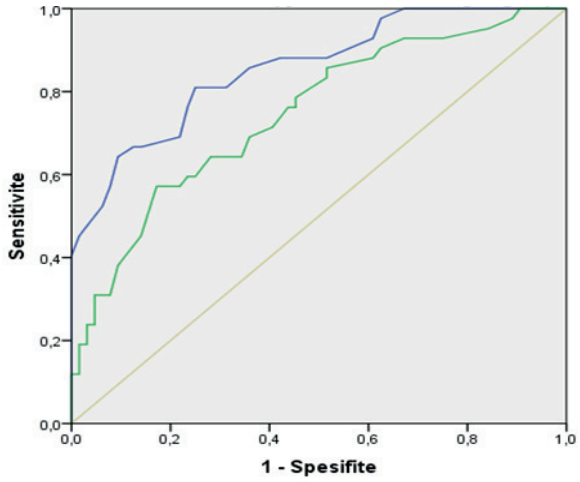
CI; Confidence Interval

ROC analysis was performed for the independent predictive factors of age and FBA. Cut-off values, AUC, sensitivity, specificity and 95% confidence intervals were calculated and the ROC analysis graph was created. The cut-off and AUC values for age and FBS were 36.5 years and 0.856 and 102.5 g/dL and 0.746, respectively (Table 3 and Figure 1).

Table 3. Results of ROC (Receiver Operating Curve) analysis of predictive factors

					%95 CI	
	Cutoff	AUC	Sensitivity	Specificity	Lower	Upper
Age	36.5	0.856	0.750	0.810	0.784	0.928
FBS	102.5	0.746	0.828	0.571	0.651	0.842

AUC; Area Under Curve



ROC; Receiver Operating Analysis, FBG; Fasting Blood Glucose, AUC; Area Under Curv

Figure 1. ROC curve. AUC values of age (blueline) and FBG (green line) (0.856, 0.746, respectively)

DISCUSSION

According to the modified NCEP ATP III (National Cholesterol Education Program Adult Treatment Panel III), metabolic syndrome is defined as patients with at least 3 of the following components: abdominal obesity (waist circumference measurement -varying according to ethnicity- of 90 cm or more in males and 80 cm or more in females or BMI ≥25 kg/m2), hypertriglyceridemia (triglyceride ≥1.7mmol/L), low HDL cholesterol level (HDL cholesterol ≤1.03 mmol/L for males and≤1.29 mmol/L for females), increased blood pressure (systolic blood pressure ≥130 mm/Hg and/or diastolic blood pressure≥85 mm/Hg or daily antihypertensive medication use) and disrupted fasting glucose values (fasting plasma glucose ≥5.6 mmol/L) (5). MetS is a situation causing many mortal and morbid disease like diabetes mellitus, cardiovascular diseases, atherosclerosis and stroke. It is long known that there is a positive correlation between the increase in metabolic syndrome components with male sexual health, especially increased erectile dysfunction. Some studies in recent times have researched connections with PE and identified positive correlations between some metabolic syndrome components and PE occurrence (6).

Bolat et al. identified metS at rates of 51% in the PE patient group, while the metS patient rate was 24% in the control group. Apart from diastolic blood pressure, there were negative correlations between metS components and IELT; in other words, an increase in PE occurrence. Additionally, there were positive correlations found between PE-DT score and metS components, apart from fasting blood sugar and HDL level; in other words, again an increase in PE occurrence. After adjusting according to age and testosterone level in logistic regression analysis, apart from blood pressure and HDL values, the other metS components were identified to be clear risk factors for PE occurrence and it was reported that metS was a risk factor for acquired PE (7). Jet et al. identified the increase in metS components was associated with a reduction in Male Sexual Health Questionnaire for Ejaculatory Dysfunction (MSHQ-EJD) score and increased ejaculation anxiety score. They proposed some hypotheses that metS (i) causes depression which accelerates PE occurrence, (ii) causes variations in the only primary organic cause of PE of serotonergic receptor functions, and (iii) increases tissue inflammation causing prostatitis and due to prostatitis contributes to PE formation (8). Similarly, Gao et al. (9) in a population survey in China identified metS connected diseases like hypertension, diabetes mellitus and heart diseases were higher in acquired PE patients than in the group with lifelong PE. In our study, apart from BMI values, all metS components were significantly higher in the acquired PE patient group compared to the lifelong PE group, as expected. In fact, fasting blood sugar was a clear predictive factor for PE formation on logistic regression analysis. In our study, in parallel to the literature, we identified acquired PE patients had more metS components; in other words, comorbid problems, compared to the lifelong PE group.

It is a reality known for a long period that vascular and neurologic causes in DM or hyperglycemic patients cause ED development. But the association between DM and PE has not been fully enlightened and there are very few studies researching this association (15). In population prevalence studies researching the association of DM and PE, the DM group was reported to have statistically significantly more PE patients compared to the control group (10,11). Owiredu reported the association of DM and PE was 56.6% (12), while Majzoub reported 78.9% (10). A prospective multicentric study by Corona et al. (13) reported nearly 28% of diabetics had PE. El-Sakka et al. (14) reported that PE was more commonly observed in 10-year DM patients, and additionally 10 times more PE was observed in patients with HbA1c≥7% compared to patients with HbA1c<7%. In our study, we could not compare hyperglycemia or DM prevalence in males with PE and males without PE due to not including a control group without PE, but mean FBS was significantly higher in the APE group compared to the LPE group. We identified FBS was a predictive factor for the disease with logistic regression analysis (AUC: 0.746). ROC analysis found the cut-off value was 102.5 g/dL. In other words, in parallel with the literature, we can say high FBS increased the incidence of acquired PE disease in our study.

Microvascular complications like diabetic neuropathy are common in DM. For ejaculation, the integration of central and peripheral neurotransmitters and the autonomic nervous system is required. Probably, the possible connection between DM or hyperglycemia with PE may be due to neurogenics via neurotransmitters and psychological function disorder. Nitric oxide (NO) is a key molecule at many metabolic, vascular and cellular levels. Animal experiments have reported that reducing the sympathetic nervous system activity inhibiting seminal emission benefits PE and that in diabetic neuropathy situations, the increased insulin resistance disrupts the

NO metabolism, which normally has positive effects on ejaculation (10). Additionally, there are hypotheses that DM causes hyposensitivity of the 5-HT2C serotonin receptor in the presynaptic area. Animal studies have found that another neurotransmitter effective on ejaculation of dopamine reduces in insulin resistance situations and increases when insulin sensitive situations occur. Another cause blamed is the association with PE in DM patients. These patients wish to finish before the erection is lost when they enter sexual relations or due to performance anxiety and this psychological conditioning situation causes premature ejaculation (13).

In recent times, a few epidemiological studies are encountered reporting that the tendency toward PE is higher in patients with erectile dysfunction (15). Jeh et al. (8) stated that IIEF questioning found overall satisfaction (OS) was related to acquired PE and that there was partial, but not full, association between ED and PE. PE patients monitored while using sildenafil for 8 weeks stated that in spite of no improvement in PE status, OS and ejaculatory control perception increased and there was shortened refractory time before secondary erection (4). Vivekanandan et al. (11) found the association of ED with PE was significant in a population survey (P<0.001). They reported that the use of dapoxitine and miradenafil in lifelong PE patients improved IELT and total sexual activity time compared to use of dapoxitine alone. We found the IELT score was significantly low as a result of the high metS components preparing the way for probable ED formation in the acquired PE patient group. In conclusion, though not proven, we think the pathophysiological process causing acquired PE causes ED or the event chain causing ED leads to formation of PE. A meta-analysis study by Corana et al. (13) observed more ED in males with PE (OR3.68); additionally, PE patients who were elderly, had low educational level and unstable sexual life had increased ED rates. Malavige et al. (16) identified 42% PE among diabetics in a population survey study and reported that as ED severity increased, the association with PE increased (Odds ratio [OR] = 4.41). Tsai (17) reported that ED patients had significant PE association compared to non-ED patients, while the prevalence of ED in PE patients was greater compared to those without PE (Odds ratio 12.7). Men without ED had elevated adjusted Odds ratio for PE compared to those with ED (mild ED Odds ratio 7.2, severe ED Odds ratio 36.7).

The connection between PE and lower urinary tract discomfort or LUTS was researched with the question 'how often do you experience unwanted premature ejaculation during sexual relations?' for prevalence of PE among patients in the Epi-LUTS (LUTS epidemiology) study. The results of the study reported some LUTS parameters were associated with PE. It is known there is a positive correlation between prostatitis with PE prevalence, with IELTS known to lengthen after antibiotic treatment for prostatitis. Jeh et al. found correlation between pain and voiding subscale scores on the NIH-CPSI(National institute of health –chronic prostatitis symptom index) with acquired PE risk, though with low Odds ratio values (1.07 and 1.17). It is proposed that PE may develop due to excess stimulation of nerve paths effective on semen emission and ejaculation causing prostatitis. Zhang (18) in a study of those aged 40-59 years identified higher IPSS in PE patients compared to non-PE patients. They showed a clear correlation between the self-reported IELTS in the four PE types with IPSS (P<0.001). This correlation was reported to be stronger in the acquired PE group (adjusted r = -0.502, P < 0.001). In our study, we could not determine the prostatitis history of any of our patients but the IPSS score was higherin the acquired PE group with higher mean age. From this, we can say elevated IPSS was correlated with acquired PEin our study.

In this study, the age factor was an effective predictive factor for PE development on logistic regression analysis and ROC analysis found the age cut-off value was 36.5 years (OR: 1.14). In other words, the probability of PE development was higher for males over 36.5 years of age, with lifelong PE disease identified more intensely below this age. Population screening in Italy reported premature ejaculation was observed more frequently in males 40 years and younger (19). Contrary to this, a multi-country epidemiological study screened those from 25-54 years and found the PE development rate was nearly 21-23.6% in all age groups in all countries and reported age was not important for PE development. Tsai et al. (17) reported a positive correlation between PE prevalence in a population survey and IELT <1 min rate with the increase in age. Additionally, there are studies reporting acquired PE patients have older ages compared to the lifelong PE group, as in our study (9).

Testosterone is one of the most effective key players in male sexual function in the central and peripheral nervous system. While low levels of testosterone are observed to be associated with obesity, metS and type 2 DM, high testosterone levels are suspected to be connected with PE. Testosterone suppresses serotonin known to be a neuromodulator preventing ejaculation causing secondary PE. Serotonin is released from the brain stem, hypothalamus and spinal cord and has inhibitory effect on ejaculation. It is reported that polymorphism of androgen receptor genes contributes to PE development with testosterone levels. Males with long CAG repeats on the androgen receptor gene are reported to have high testosterone levels, reduced IELT and increased PE-DT and this situation is stated to cause more severe PE (20).

Testosterone has central and peripheral effect on ejaculation. Testosterone-dependent PDE-5 expression and activity is found in other regions of the male genital system like the vas deferens with critical effect on semen emission and ejaculation. Some animal experiments have reported that hypogonadism or testosterone deficiency reduces biologically active PDE-5 in the vas deferens, this situation reverses when testosterone is administered. The association of hypogonadism with delayed ejaculation may be due to increased inhibitor nitrergic material in

smooth muscle cells of the male genital system (2). Additionally, low amounts of 5-HT were identified in the brains of animals administered testosterone for long durations. In our study, the testosterone level in acquired PE patients was significantly low compared to the lifelong PE group and we think this situation may be connected with age, rather than causing acquired PE.

LIMITATIONS

Limitations of our study include it being retrospective, the low number of patients in the groups, the lack of study of thyroid hormone level, oxytocin hormone and neurotransmitter values like dopamine considered to affect ejaculation and the lack of waist circumference measurements used with BMI for the obesity parameter in metS. There is a need for multicentric prospective studies with larger patient numbers in the future to enlighten the etiopathogenesis of PE disease.

CONCLUSION

PE is the most common reason for attending clinics due to sexual disease in males. Lifelong PE formation is not caused by environmental or medical causes so we still have no recommendations for treatment in this group other than SSRI or topical local anesthetic agents. However, we now know metS components and LUTS prepare the way for acquired PE formation. As a result, though it appears like the same disease after occurrence, it seems that treatment of acquired PE should involve the resolution of these causes.

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